BELGIAN GUIDELINES
ON THE DIAGNOSIS AND MANAGEMENT OF LATENT TUBERCULOSIS INFECTION

2019

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ABBREVIATIONS

AIDS	Acquired immunodeficiency syndrome
BCG	Bacillus Calmette-Guérin
BELTA	Belgian Lung and Tuberculosis Association
cART	Combination antiretroviral therapy
CD4+	Cluster of differentiation 4
CDC	Centers for Disease Control and Prevention
CFP-10	10 kDa culture filtrate antigen (antigen produced by *M. tuberculosis*)
CMI	Cell Mediated Immunity
DOT	Directly Observed Therapy
DST	Drug Sensitivity Testing
ECDC	European Centre for Disease Prevention and Control
ELISA	Enzyme-linked immunosorbent assay
ERS	European Respiratory Society
ESAT-6	6 kDa early secretory antigenic target (antigen produced by *M. tuberculosis*)
FARES	Fonds des Affections Respiratoires
G6PD	Glucose-6-Phosphate Dehydrogenase
HIV	Human immunodeficiency virus
IFN-γ	Interferon gamma
IGRA	Interferon gamma release assay
INH	Isoniazid
IU	International unit
IUD	Intrauterine (contraceptive) Device
LTBI	Latent tuberculosis infection
M.	*Mycobacterium*
MDR	Multidrug-resistant
MTB	*Mycobacterium tuberculosis*
NICE	National Institute for Health and Care Excellence
NTM	Non-tuberculous mycobacteria

PBMC	Peripheral blood mononuclear cells
PLHIV	People living with HIV
PPD	Purified protein derivative
PZA	Pyrazinamide
QFT	Quantiferon
RMP	Rifampicin
SHC	Superior Health Council
TB	Tuberculosis
TNFα	Tumor necrosis factor alfa
TST	Tuberculin skin test
VRGT	Vlaamse Vereniging voor Respiratoire Gezondheidszorg en Tuberculosebestrijding
WHO	World Health Organization

1. INTRODUCTION

The purpose of the Belgian guidelines on the Diagnosis and Management of Latent Tuberculosis Infection (LTBI) is to provide guidance on:

- how to identify and prioritize at-risk population groups who would benefit from LTBI testing and treatment;
- how to provide LTBI treatment to those who need it.

The present guidelines are an update of an earlier document, published in 2003 (1). They are based on the WHO (2), ERS (3) and NICE (4) guidelines on the management of LTBI, published in 2015.

These guidelines contain recommendations on the identification of individuals for LTBI testing and treatment, the algorithmic approach to test and treat LTBI and the treatment options. The recommendations are mainly based on critical appraisal of the evidence, the balance of the anticipated benefits and harms, the values and preferences of individuals and health care providers as well as resource implications.

The overall logical approach for the development of the guidelines and the formulation of the recommendations was as follows: 1) identification of the risk groups that are eligible for screening and subsequent treatment of LTBI; followed by 2) evaluation of the accuracy and drawbacks of the screening tests; and 3) the effectiveness and harms of the treatment regimens.

Using a Delphi method, the members of the LTBI Working Group of the Scientific Committee Tuberculosis of BELTA were consulted on unresolved issues after a first revision of the Belgian 2003 guidelines. A series of Internet-based consultations were organized, and all participants had ample time to respond to the questions. Questions were asked in PICO format (Population/Patient, Intervention/Indicator, Comparator/Control, Outcome) wherever possible. The results were used to update the guidelines. These guidelines were then revised and commented by each participant individually before a final stakeholder meeting at the end of 2016. Since then, additional evidence has become available and new international guidelines (5) and recommendations (6) have been published. While these were being integrated into the present recommendations, the ECDC published a review of the available evidence related to LTBI in 2018 (7). Most evidence was graded as “weak”, which explains why it has been a very time consuming process to develop the present guidelines and why the recommendations are not always clear cut.

When using these guidelines, it should be borne in mind that decisions related to the diagnosis and treatment of LTBI are mainly based upon individual assessment, carefully balancing all available factors, tests and their results being only one element among many.

2. THE NEED TO ADDRESS LTBI

Belgium is classified as a low-incidence country according to the definition of the WHO (8) because the annual incidence of TB is less than 10 per 100,000 inhabitants. In low-incidence countries, TB is concentrated in recent contacts of infectious TB cases and in vulnerable groups such as those with low socio-economic status, homeless persons, newly-arrived migrants from high-incidence countries, people living with HIV/AIDS, people with drugs or alcohol dependency, prisoners, older adults and children, particularly those below 5 years of age (see table 2 in 3.1.1). Also, there is a geographic concentration in Belgium's large cities such as Brussels, Liège, Antwerp and Charleroi.

The "2015 WHO Global Tuberculosis Strategy" targets a reduction in the global incidence of TB by 90 % between 2015 and 2035 (9). To reach this objective, both high-burden and low-burden countries must intensify their efforts to prevent TB. The lowest burden countries, including Belgium, must progress to pre-elimination (< 10 cases per million inhabitants) and then move to an elimination of TB as a public health problem (< 1 case per million inhabitants). Early diagnosis and adequate treatment of active TB cases will not be sufficient to reach these goals. Individuals that are latently infected represent a large reservoir of potential future active TB cases that must also be addressed. Indeed, the preventive treatment of LTBI decreases the risk of developing an active clinical disease, reducing the risk of transmission and thus contributing to the eradication of the disease.

Between a quarter and a third of the world's population is estimated to be latently infected with *Mycobacterium tuberculosis* (10). Despite the extent of infection, unfocused population-based testing is not cost-effective or useful and leads to unnecessary treatment. Efforts must be made to identify asymptomatic carriers, i.e. those that are at greatest risk of reactivation and subsequent progression to symptomatic and contagious TB. Thus, TB testing activities should be conducted only among high risk groups, with the intent to treat if LTBI is detected. Once TB disease has been excluded, treatment of LTBI should be offered to patients unless medically contraindicated (5).

Only in countries with a low TB burden, where ongoing transmission is minimal, TB from remote infection is thought to be a substantial contributor to the active TB burden. Importantly, most such TB cases do not generally result in major disease outbreaks, probably as a result of well-functioning public health systems (that include LTBI screening and treatment) (11).

MTB infection is acquired by inhalation of infectious aerosol particles released from infected contacts. Most individuals, who inhale MTB, mount an effective immune response that prevents the immediate development of clinical disease after primary infection. A spectrum of immunological responses results in a wide range of subclinical infection states varying from viable bacilli that actively replicate without causing disease to clearance of infection accompanied or not by the establishment of memory responses to MTB antigens. As such, clinical latency occurs when the host immune responses control bacterial replication, called LTBI stage, and it is only when bacterial replication is no longer kept in check by the immune response that clinical disease does occur. Figure 1 illustrates the pathogenesis of TB infection, but it should be realised that considerable gaps

remain in the available knowledge. A detailed understanding of the real nature of what is commonly called "latent TB infection" is lacking.

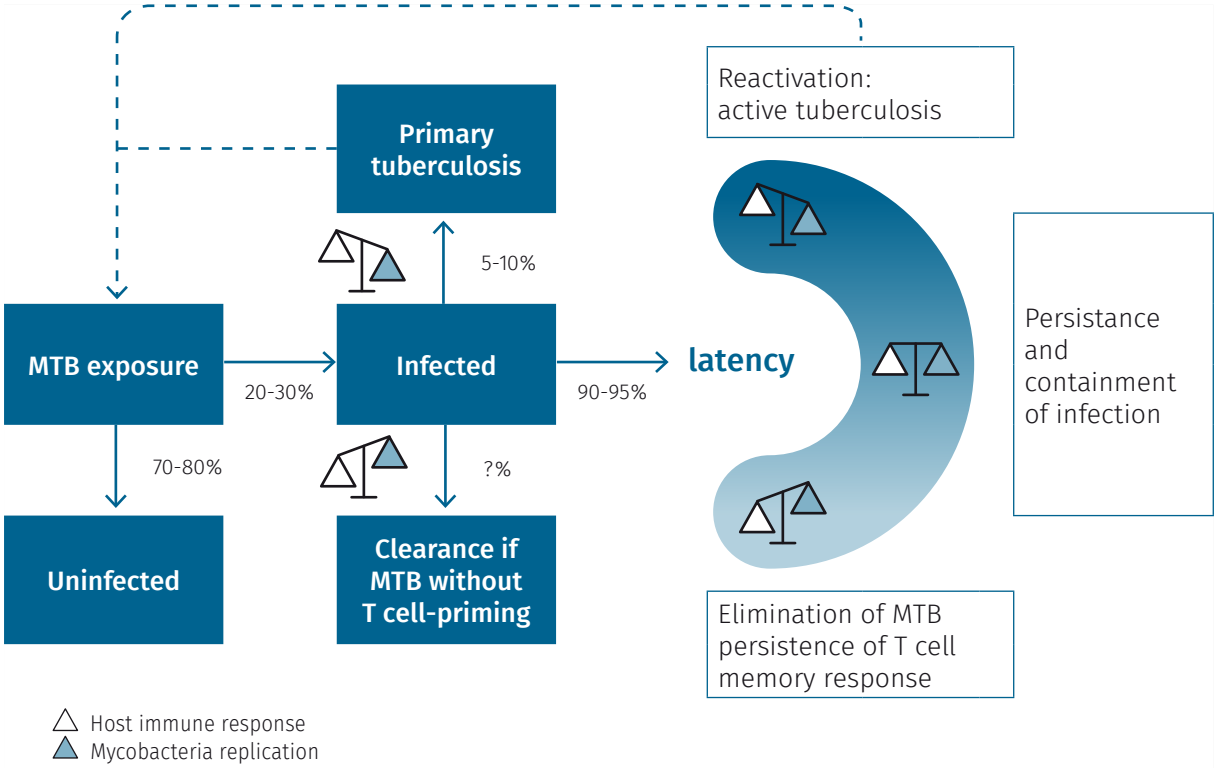


Figure 1. Pathogenesis of TB infection, adapted from reference (12)

The lifetime risk of TB reactivation for a person with documented LTBI is estimated to be 5–15 %, with the majority developing TB disease within the first five years after primary infection (12). In a population-based cohort study using molecular typing of MTB, the probability to fall ill within one year was 45 %, within two years 62 % and within five years 83 % (13). If no disease develops within five years, the remaining lifetime risk might be as low as 2 %, and 0.5 % after ten years (14). The most recent analysis of multiple longitudinal epidemiological studies, however, shows that the majority of TB disease manifests itself soon after infection, with disease rarely occurring more than two years after infection (11). Although bacterial, host and environmental factors will together determine the likelihood of progressing from latent infection to clinical TB, it is the immunological status of the host that is of particular importance (15).

Immunodeficiency, and in particular advanced HIV infection with severe immunodepression, is a major risk factor for the development of active TB. Primary TB, *M. tuberculosis* re-infection and re-activation are all more frequent in this high risk group. The advent of combination antiretroviral treatment (cART) for the treatment of HIV-infection has dramatically changed the risk for active TB with a steep 44 % to 80 % drop in TB incidence, depending on the setting (16) (17). In non-endemic countries, the risk of active TB in HIV-infected patients under cART remains higher than in the general population but with low incidence rates (1.64/1,000 person-years) (18).

The reactivation of TB can be averted by preventive treatment. Currently available regimens for the treatment of LTBI have an efficacy ranging from 60 % to 90 %, the protection of which can

last for up to 19 years for subjects living in low burden settings (19). The potential benefit of treatment needs to be carefully balanced against the risk of drug-related adverse events. For infected individuals in population groups with a high risk of progression to active disease, the anticipated benefits are usually greater than the potential harms. It is thus important to identify these individuals (5).

A recent large meta-analysis identified major losses at several steps in the cascade of care for LTBI (20). Improvements in the management of LTBI will need programmatic approaches to address the losses at each step in the cascade. Greater attrition occurred for completion of testing (35 %), completion of the medical evaluation (56 %), recommendation for treatment (65 %), and completion of therapy if started (19 %). Steps with fewer losses included receiving test results, referral for evaluation if test positive, and accepting to start therapy if recommended. Factors associated with fewer losses were immunocompromising medical indications, being part of contact investigations, and use of rifamycin-based regimens.

Many reasons were related to the loss along the cascade. These reasons include, but are not limited to, immigration status, the absence of health care coverage, language or culture barriers, incomplete knowledge of the health care worker about the need for LTBI treatment, older age (i.e. > 35 years) and the perception of risk and severity of LTBI (20).

These findings suggest a need to properly define the goal of LTBI testing, for each patient or group, and to design less toxic and shorter treatment regimens to increase adherence to treatment.

Immunodeficiency, and in particular advanced HIV with AIDS, is an important risk factor for the development of active TB. The immunodeficiency disorders requiring LTBI screening are listed in the present guidelines. In addition, a specific approach regarding testing indications (3.1.4.c), choice of test (3.3.4) and LTBI treatment (4.1.2.b) is proposed for PLHIV. LTBI management in other patients whose cell-mediated immunity has been compromised (e.g. anti-TNFα candidates, hemodialysis patients, transplant recipients etc.) will vary a lot depending on the underlying disease or the kind of treatment they receive. The present guidelines offer no specific recommendations regarding such patients, as they often need to be managed on a case by case basis. If in doubt about the management of LTBI related issues in immunocompromised hosts, it may be wise to seek expert advice.

3. LTBI TESTING

3.1. WHO NEEDS TO BE TESTED FOR LATENT TUBERCULOSIS INFECTION

3.1.1. Risk factors for LTBI evolving into active TB

Although most latently infected individuals control the infection and are asymptomatic, the risk of progression to active TB remains. It is, therefore, crucial to identify those at the highest risk of progression to active TB, and who would, therefore, benefit from closer monitoring and preventive treatment. These at-risk subjects are those with a recent exposure to TB and/or who present a specific risk factor for developing active TB. Table 1 shows the principal risk factors to consider, while Table 2 shows the age related risk.

Table 1. Risk of developing active tuberculosis in individuals infected with MTB. Adapted from (21) (22)

Risk factor	Relative risk of developing TB compared to an individual without risk factor
High risk	
AIDS	110–170
HIV-positive, untreated with antiretroviral therapy	50–110
Solid organ transplantation requiring immunosuppressant therapy	20–74
Jejunoileal bypass	27–63
Silicosis	30
Chronic renal failure/hemodialysis	10–25
Hematological malignancy (leukemia, lymphoma)	16
Carcinoma of the head or neck and lung	2.5–6.3
Close contact with recent tuberculosis infection (≤ 2 years)	15
Apical fibronodular and other fibrotic lesions on chest X-ray	6-19
Receiving anti-TNFα treatment	1.5–17
Children < 3 years	> 10
Moderate risk	
Corticosteroids ≥ 15 mg prednisolone equivalent/day for > 2–4 weeks	4.9
Diabetes mellitus	2–3.6
Children aged 3-4 years	> 3
Slightly elevated risk	
Smoking	2–3
Excessive alcohol use	3
Underweight	2.0–2.6
Solitary lesion on the chest X-ray	2-2.6

Table 2. Risk of active TB in immunocompetent children following LTBI (23)

Age at primary infection	Risk of pulmonary disease or mediastinal lymphatic disease %	Risk of meningeal or disseminated tuberculosis %
< 12 months	30–40	10–20
12–24 months	10–20	2–5
2–4 years	5	0.5
5–10 years	2	< 0.5
> 10 years	10–20	< 0.5

3.1.2. Groups to be tested for LTBI

The group listings below are based on the 2015 WHO guidelines (2) updated with the 2018 ECDC recommendations (7).

Systematic testing and treatment of LTBI are strongly recommended in:
- household contacts or close contacts of pulmonary TB cases, especially those contacts less than five years of age;
- people living with HIV at high risk of developing active TB (24);
- patients initiating immunosuppressive therapy[1], including but not limited to anti-tumour necrosis factor (anti-TNF) treatment, anti-CD52, anti-CD20, patients preparing for organ transplantation...;
- patients undergoing dialysis.

Testing and treatment of LTBI should be considered for:
- prisoners;
- high-risk immigrants from high-burden countries, i.e. asylum seekers aged less than 5 years and pregnant women (see Annex 1 for list of high-burden countries);
- patients presenting with silicosis (to be assessed on individual basis);
- patients with fibrotic lesions (see 3.1.4.d);
- people traveling to/living in high-prevalence countries (see 3.1.4.e);
- health care workers and other professionals in contact with person from high risk groups (see 3.1.4.f).

In general, testing for LTBI is not recommended for people with diabetes, people with harmful alcohol use, tobacco smokers, and underweight people provided they do not fit in the above recommendations.

1 All immunodiagnostic tests should preferably be performed up to one month before immunosuppressive therapies are initiated or intensified, so that a person testing positive may still be treated for at least a month before starting immunosuppressive drugs.

3.1.3. Testing in children [2]

During contact tracing, children deserve specific attention because they are at high risk of developing active TB, as mentioned above (see Table 2). The risk of disease is greatest close to the time of infection. Those under 5 years of age have a particularly increased risk of severe forms of disease. Over the period 2010-2017, 51.6 % of the children diagnosed with TB in Belgium were less than 5 years old [3]. If a child aged less than 5 years tests negative on first LTBI testing, start windows prophylaxis up to the time of retesting (8 weeks after the last exposure to the index case) (see 4.1.2).

If the index case is a child, contact screening might seem less useful because children do not have highly infectious forms of TB; however, when a child less than 5 years of age develops TB, it is likely that the infection was acquired from a person in the household. The rationale for assigning high priority to contacts of index cases < 5 years of age is to find the source of the infection (25).

In children, prior BCG vaccination is never a contraindication for LTBI testing (26). A single BCG vaccine at birth usually leads to a positive TST that wanes over the next decade (21) (27). In children who received vaccination during the newborn period (days 1 to 28), 85 % lost reactivity within two to three years (28). By the age of 10 years less than 1 % of children had a TST of 10 mm or greater (29).

3.1.4. Testing in other specific situations

3.1.4.a. Pregnancy and postpartum

Pregnancy does not constitute a risk factor for disease reactivation, but TB during the first 3 months of postpartum may involve more severe disease, including immune reconstitution inflammatory syndrome (IRIS) and a high mortality rate (30).

For women at risk of TB, pregnancy provides an important opportunity to screen for LTBI. As women are already in care, acceptance of LTBI testing and chest radiography is high. During postpartum, acceptance will be lower and particular attention must be given to appropriate follow-up.

3.1.4.b. Ageing persons

Several studies have shown that reactivation and transmission of TB is higher among institutionalized elderly compared to those living at home (31).

The Belgian Superior Health Council (SHC) recommends that any new residents of a retirement home be free from contagious TB in order to limit the risk of transmission within the facility.

2 Child: aged 0 - 15 years

3 Data from the national tuberculosis registers 2010-2017:
https://tuberculose.vrgt.be/informatiebank?term=&cid%5B23%5D=23 (Flemish)
https://www.fares.be/fr/tbc-publications-rapports-epidemiologiques/ (French)

Systematic X-ray screening is not recommended, but all new residents need to be checked for any history or signs of TB, particularly if they belong to a risk group. Only in the presence of any clinical and/or anamnestic presumption of TB, an X-ray of the thorax should be performed.

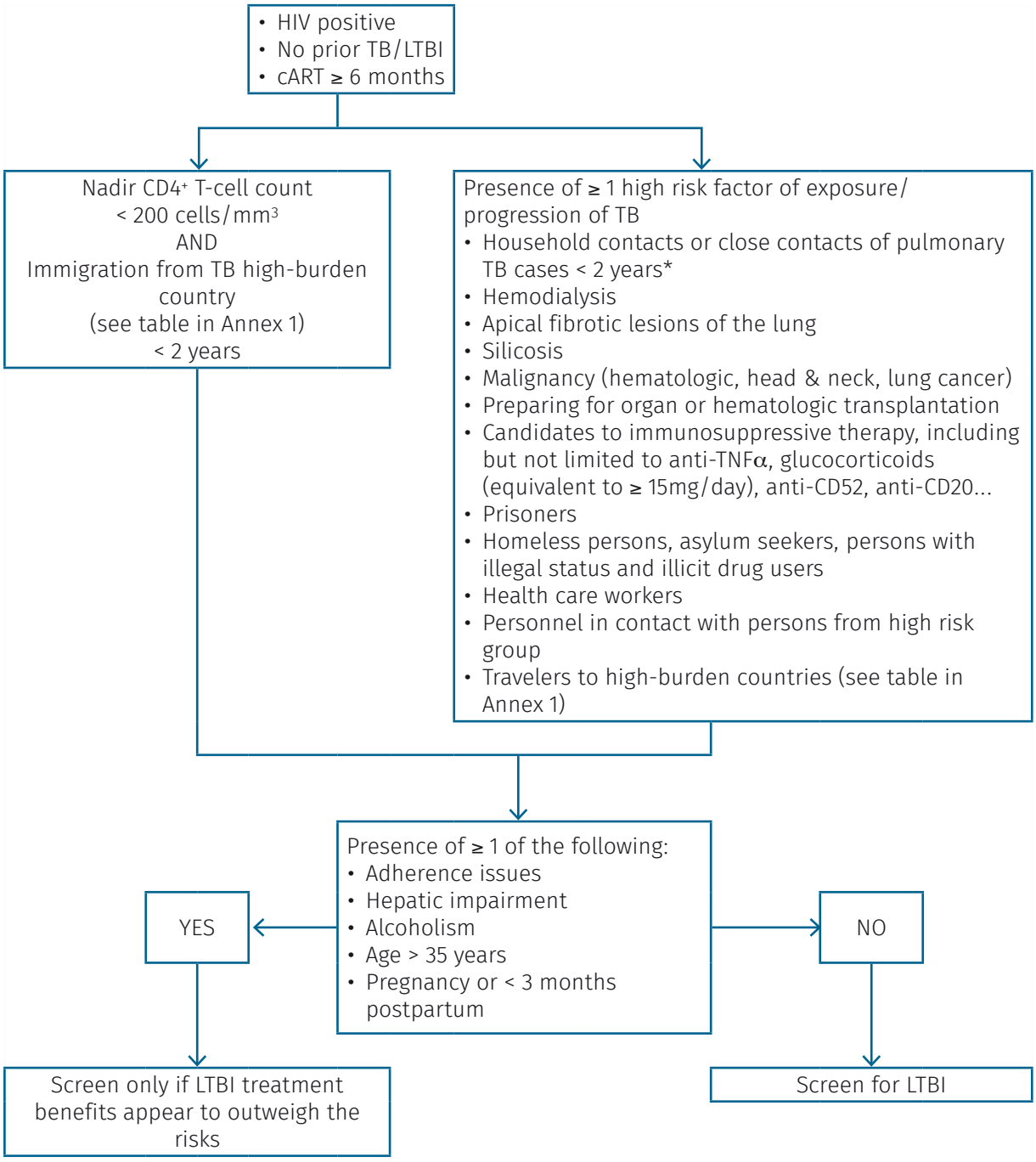
Universal screening for LTBI at entry in a facility is not recommended:
- LTBI testing must lead to a decision to treat preventively in the event of a positive outcome. However, the "intention to screen is intention to treat" principle is rarely applied in view of the increased hepatotoxicity of isoniazid (INH) with age and the greater likelihood of a long-standing infection (and thus reduced chance of reactivation);
- if screening is done by TST, the elaboration and reading of the test are not easy in the elderly (thin skin and withered). Moreover, the interpretation of TST is made difficult because of the booster effect which is more frequent in people over 55. In the absence of reaction, the test should be repeated 2 weeks later to avoid false negatives (see 3.4.1.h);
- screening by IGRA on arrival in the institution is not advised in the Belgian context. The literature on the use of these tests in the elderly is very limited (31).

3.1.4.c. Persons living with HIV (PLHIV)

Treatment for LTBI has shown to decrease risk of active TB in HIV-infected persons, with an additional benefit to cART (32) (33) (34). However, defining a LTBI screening and treatment strategy for PLHIV is far from straightforward as many issues arise. Firstly, there has been no prospective study demonstrating the additional benefit of LTBI treatment to cART in non-TB endemic settings, as all studies have taken place in sub-Saharan Africa (32) (34). Secondly, the sensitivity of TST and IGRA is reduced in the context of HIV-infection, with a sharp fall with declining $CD4^+$ count (35). This is particularly problematic as it is the people with the lowest $CD4^+$ count that are at the highest risk of developing active TB. Thirdly, there are major discrepancies in the national and international recommendations on the topic, including choice of screening tool(s), timing of screening, repetition or not of screening during follow-up, and choice of drug regimen.

Taking into account these different issues, the following key points, adapted from the recently published LTBI guidelines endorsed by the Belgian AIDS reference centres, are suggested for LTBI screening in PLHIV (24):
- Target population:
  - screening for LTBI should be considered for HIV-infected persons with a baseline $CD4^+$ T-cell count below 200 cells/mm^3 AND with history of immigration from a high-burden TB country (see table in Annex 1) in the past 2 years;
  - screening for LTBI should be considered for HIV-infected persons with ≥ 1 high-risk factor of exposure to *M. tuberculosis* or progression to active TB (see figure 2).
- Timing of screening:
  - screening for LTBI should be performed 6 months after cART initiation;
  - patients who have already been on cART for a longer period of time and have never been screened, should only be screened if they enter the target group defined above.
- HIV-infected household contacts or close contacts of pulmonary TB cases: should be tested right away (see 3.4.1.b) and must be treated immediately for LTBI, after exclusion of active TB, regardless of LTBI screening result (see 4.1.2.b) and without postponing until 6 months of cART have been given.

Figure 2 summarizes the approach in PLHIV.



* Treat immediately for LTBI regardless of LTBI test result (see 4.1.2.b)

Figure 2. When to screen for LTBI in PLHIV (based on reference 24)

3.1.4.d. People with fibrotic lesions on chest X-ray

Little information is available in the recent literature on the statistics of LTBI in fibrotic lesions, and references cite the major studies performed in the 1970s (36) (37) (38).

Fibrotic scars are defined as lesions on chest X-ray larger than 5 mm, suggestive of old untreated pulmonary TB in patients without a previous diagnosis or of insufficiently treated pulmonary TB. They are described as "well-defined" or "radiologically dense", and consist of nodules, fibrosis-like linear images with or without retraction and bronchiectasis in the upper lobes and with no evidence of alveolar component and/or cavitations. Calcified primary complex, localized pleural thickening and/or isolated lateral costophrenic angle blunting have also been described, but these may be considered less significant and are excluded from some definitions (36) (39).

Fibrotic lesions are important for three reasons (36):
1. there is a risk of TB reactivation in the future;
2. misdiagnosis of fibrotic lesions can mask smear-negative active TB, and there is a danger of starting LTBI single-agent therapy that may lead to acquired resistance or failure to treat. Conversely, misdiagnosis of fibrotic lesions as active TB may result in the administration of unnecessary and potentially toxic medications;
3. fibrotic lesions on chest X-ray are not always indicative of TB and may be confounded with other unrelated disease entities that may present with the same radiological patterns.

The risk of reactivation of fibrotic lesions depends on a series of factors, being (36):
- the maturity of the lesions: the risk of TB reactivation falls progressively over time;
- the lifetime risk of reactivation of fibrotic lesions diminishes significantly with age. Lesions are more likely to be old in the elderly, and given their reduced life expectancy there is less likelihood of reactivation. Conversely, in young subjects, lesions are more probably recent and this, along with longer life expectancy, leads to a higher risk of reactivation. In children, the concept of fibrotic scarring is complicated, since lesions can be presumed not to be old and should rather be considered as active TB;
- TST induration diameter is correlated with reactivation, especially if more than 15 mm. Also, a higher value of IGRA testing is correlated with TB reactivation (40);
- if TST conversion is recent, there is a higher chance of active TB;
- the more extensive the scarring, the greater the bacillary load of the initial TB infection. If lesions with cavitation, non-calcified adenopathies, and/or pleural effusion are present, even if smear or culture negative, active disease should be excluded.

The differential diagnosis of fibrotic lesions includes all pulmonary processes that may present with radiological features that look like active pulmonary TB. Careful clinical evaluation and appropriate complementary examinations must be used to rule out an alternative diagnosis, taking into consideration risk factors for active TB (36).

In the absence of clinical symptoms suggesting active TB, a X-ray follow-up should be performed after three months (and even one month if lesions are extensive), while waiting for the culture results (36). If LTBI testing is negative, an alternative diagnosis should be sought, and appropriate clinical follow-up done.

3.1.4.e. Travelers and/or expatriates

Travelers can be subject to screening for LTBI under specific circumstances. Indeed, a conversion of TST test has been observed at a rate of 3 to 4 % in long-term travelers and expats from the Netherlands and United States and can reach as high as 12 % in person employed or volunteering in health care settings (41). Nevertheless, screening for LTBI should only be carried out among travelers at greatest risk of acquiring TB (e.g., volunteers, long-term adventurous travelers, backpackers...) (42). Another group deserving particular attention are children born in Belgium who travel to an endemic country for family visits.

Travelers fulfilling the following criteria can be identified as candidates for LTBI screening:
- ≥ 1-month travel which includes an increased risk of exposure, specifically direct contact with risk categories such as patients, prisoners, homeless persons, or refugees;
- ≥ 3-month travel to a region with a TB incidence of > 400/100,000 inhabitants;
- ≥ 6-month travel to a region with a TB incidence of 200-399/100,000 inhabitants;
- ≥ 12-month travel to a region with a TB incidence of 100-199/100,000 inhabitants.

A listing of high-burden countries according to TB incidence per 100,000 inhabitants can be consulted in Annex 1.

There is little indication that either TST or IGRA is useful in persons with a low risk of disease progression. However, documenting a negative test before exposure might help to decide whether to start preventive treatment if a conversion has occurred following exposure. Documenting TST before travel is important in travelers identified as candidates for LTBI screening after their return. Screening with a TST in a very low-risk population of travelers may result in a false-positive test, leading to unnecessary diagnostic investigations and treatment. As such, it seems prudent that any positive TST before travel is confirmed by IGRA to increase specificity (43).

If LTBI is diagnosed, the indication to start preventive treatment should be assessed on a case-by-case basis with an expert, as the risk of progression to active TB disease might be extremely low when diagnosed before the actual travel. After travel, screening for LTBI should be repeated at six weeks to 3 to 4 months after return, if LTBI test proved negative before travel (41).

3.1.4.f. Professionals with high risk of exposure to tuberculosis

In 2014, the SHC published a policy advisory report that provides recommendations regarding the prevention of TB in health care facilities (31). This document detailed the legal requirements, risk assessment for individual health care workers, the outlines of a prevention plan, the use of TST, IGRA, chest X-ray and BCG vaccination. However, the document is equally valuable and applicable for other categories of workers with a high risk of exposure to pulmonary TB, such as prison wardens, personnel in contact with asylum seekers...

The need for testing for LTBI depends heavily on the risk the employee is exposed to. There is little indication that either TST or IGRA is useful in persons with a low risk of disease progression. However, documenting a negative test before exposure might help to decide whether to start preventive treatment if a conversion has occurred following exposure.

The SHC considers four categories of risks for health care workers:

A. Employees who are exposed, on a regular basis, to many TB-infected patients or contaminated products. These include:
- hospital staff of emergency services, intensive care units, pulmonology or infectious disease departments. The personnel categories to be screened include the medical staff, maintenance staff, logistics and patient transport staff;
- personnel of the microbiology laboratory, particularly those in contact with mycobacteria;
- personnel present during autopsy.

Employees of group A should be screened upon recruitment to establish the presence or absence of LTBI and should be retested semi-annually.

B. Employees who are occasionally exposed to TB-infected patients or contaminated products. These include:
- the staff of hospital services other than those mentioned in group A;
- the staff of long-term care facilities.

Employees of group B should be screened upon recruitment to establish the presence or absence of LTBI and should be retested (at minimum) annually.

C. Staff for whom the risk of exposure is no greater than when they are off duty, such as administrative personnel working in areas restricted to personnel only.

Employees of group C should not be screened for TB infection on a regular basis.

D. Employees with an increased susceptibility to TB infection; it is the duty of the occupational physician to identify any risk factors which may increase susceptibility to TB infection and advise those members of personnel with increased susceptibility and their institutions to refrain from activities involving exposure to mycobacteria.

The exposure to MTB is a dynamic process and requires regular updates in the risk management for any of the facilities where workers can be exposed to MTB. People can be reassigned to another group because of change in risk and depending on the exposure over time in the health care facility.

Note that the timing and organization of the screening for staff of institutions that have contact with high-risk groups, such as asylum seekers or prisoners, is dependent of the risk assessment, which should be done periodically.

3.1.4.g. Other risk groups for whom LTBI testing can be considered

In 3.1.2 it has been mentioned that testing and treatment of LTBI should be considered for prisoners as well as asylum seekers aged less than 5 years and pregnant women from high-burden countries. In Belgium, specific strategies for the systematic screening of these risk groups have been developed. The particular circumstances that warrant the use of LTBI testing are explained in the respective recommendations [4].

4 **Prison strategy:**
https://tuberculose.vrgt.be/sites/default/files/Richtlijnen%20tuberculose%20gevangenissen%20Belgi%C3%AB%202007_3.pdf (Flemish)
https://www.fares.be/static/front/upload/1/upload/files/publications%20TBC/Strat%C3%A9gies/2007-Recommandations_TBC_prisons.pdf (French; baseline document)
https://www.fares.be/static/upload/1/2/Stratégie_TBC_DA_2017-complet.pdf (French; complement 2017)
Asylum seekers strategy:
https://www.fares.be/static/upload/1/2/Stratégie_TBC_DA_2017-complet.pdf (French)
https://tuberculose.vrgt.be/sites/default/files/TBC%20preventie%20bij%20asielzoekers%20-%20strategie%20voor%20Fedasil%20centra.pdf (Flemish)

3.2. WHICH TESTS ARE AVAILABLE TO SCREEN FOR LATENT TUBERCULOSIS INFECTION

Direct detection of MTB can only be achieved at the site of bacterial replication of persons suffering from active TB. Therefore, the presence of LTBI can only be detected indirectly. Currently, there are two immunodiagnostic tests available for screening LTBI, the *in vivo* TST and the *in vitro* IGRA blood tests. Both are based on the detection of memory T-cell responses to MTB antigens.

The TST is a widely used and inexpensive test that was developed over a century ago. TST is based on type IV delayed hypersensitivity skin reaction against tuberculin purified protein derivate, which is a crude mix of over 200 MTB proteins. Unfortunately, it has a poor specificity in populations vaccinated with bacilli Calmette-Guérin (BCG) and cross-reactivity with environmental NTM may occur. Importantly, the test has poor sensitivity in immunocompromised persons. Logistically, TST requires two visits, one to administer the tuberculin intradermally and 2 (even up to 5) days later a follow-up visit is needed to read the induration. The TST test is described in detail in annex 2.

IGRAs, on the other hand, measure *in vitro* immune responses to MTB antigens (ESAT-6 and CFP-10) that are not present in BCG and most NTM, thus improving the specificity of this test compared to the TST. A meta-analysis showed that, compared to TST, interferon-γ release assays have a lower rate of false negative and false positive results in patients treated with corticosteroids and those with a history of BCG vaccination (44). However, similar to TST, IGRA testing is not 100 % sensitive. In addition, IGRAs are costlier and require adequate transport conditions and laboratory facilities. The two commercially available IGRAs are the QuantiFERON®-Tuberculosis Gold-Plus (QFT®-Plus) (by QIAGEN) and the T-SPOT®.Tuberculosis assay (T-SPOT®.TB) (by Oxford Immunotec). The first measures the amount of interferon gamma (IFN-γ) released from whole blood after in-tube antigen-stimulation, whereas the second test counts the number of IFN-γ-producing cells in antigen-stimulated peripheral blood mononuclear cells (PBMCs). Both IGRA tests are described in detail in annex 3.

There is no gold standard for the diagnosis of LTBI, and all tests have been evaluated in patients with active TB. Also, these tests cannot discriminate LTBI from active TB. For this reason, before treating LTBI, active TB should always be ruled out using conventional means. In general, symptom screen for elements suggestive of TB (i.e. any one of the following: a prolonged cough, hemoptysis, fever, night sweats, weight loss, chest pain, shortness of breath and fatigue) and chest radiography offer a high sensitivity and good negative predictive value to rule out active TB (3). In children, chest radiography still identifies a small proportion of children who have findings suggestive of pulmonary TB in absence of symptoms.

3.3. HOW TO DECIDE WHICH TEST TO USE

3.3.1. General approach

In a low burden, high-income setting with a low coverage of BCG vaccination such as Belgium, routine testing with both TST and IGRA is not recommended. There is no overall preference for either TST or IGRA test, although specific situations are described below where either TST or IGRA is preferred, or both tests can be done consecutively or simultaneously.

Both tests have characteristics that need to be considered when choosing the specific test for specific populations, including - but not limited to - technical feasibility, cost, and availability (table 3). The results of TST and IGRA should be interpreted in the context of the pertinent clinical data (including age, BCG status, contact with active TB, immunodepression and other risk factors...). It is important to note that besides the scientific data, practicality and financial implications are considered relevant in determining the test strategy in individual cases and institutions.

Table 3. Characteristics of TST and IGRAs. Adapted from (45) (46)

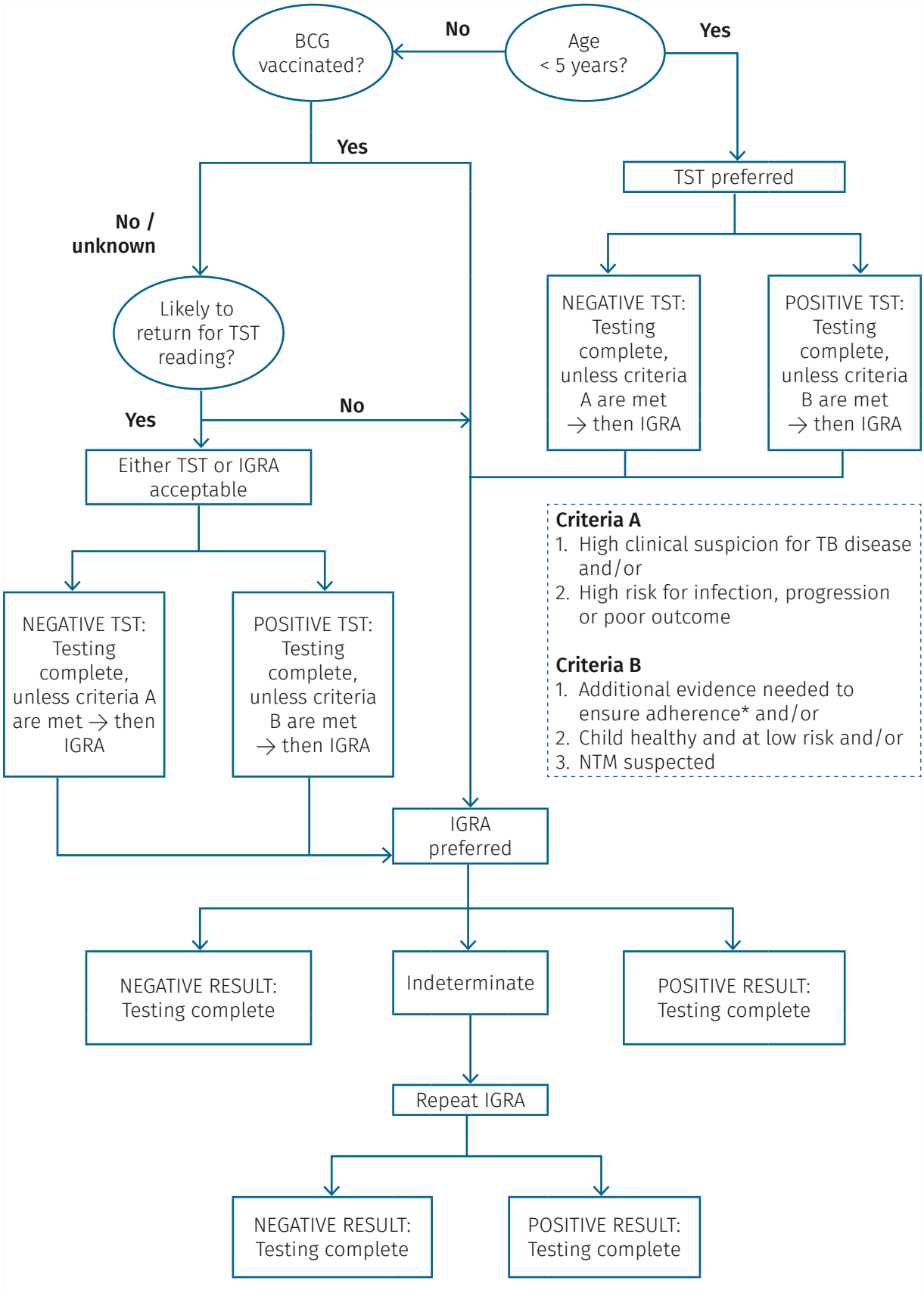
Characteristics	TST	IGRA
Number of visits	2	1
Time to read-out of results	48-120h	24h
Trained personnel required	yes	yes
Blood sampling needed	no	yes
Intradermal injection needed	yes	no
Need for laboratory equipment	no	yes
Cross-reactivity with BCG	yes	no
Cross-reactivity with NTM	yes	unlikely
Conversions /reversions	yes	yes
Distinguishes infection from disease	no	no
Secondary effects	rare	no
Risk of boosting in case of repeated testing	yes	no
Use of positive/negative controls	no	yes
Factors complicating interpretation	Inter- and intra-reader variations, boosting, use of different diameter cut off in different populations	No consensus on optimal thresholds
Material cost	low	high
Sensitivity in immunocompetent adults	70-80 %	75-90 %
Sensitivity in children (47) (48)	84 %	84 % overall 83 % QFT assays 84 % T-Spot
Specificity in adults	98 % if no BCG vaccination, 90-98 % if vaccinated in infancy, 60-80 % if vaccinated at > 1 year of age	93-98 %
Specificity in children (47) (48) (49)	88 % overall (positive defined as 10 mm) 93 % in BCG-unvaccinated 49 % in BCG-vaccinated	92 % overall 91 % QFT assays 94 % T-Spot

3.3.2. LTBI testing in children

The purpose of LTBI testing is to determine whether the child is infected with *M. tuberculosis*. The decision to test is a decision to treat. Therefore, in childhood populations testing strategies should optimize sensitivity. There is, however, no reference standard currently in existence for LTBI diagnosis in children. Several guidelines affirm that the selection of the most suitable test or combination of tests should be based on clinical data, as BCG status, history of contact with active TB or other risk factors for infection or progression of the disease.

In children with a high risk of infection or disease progression, maximum sensitivity can be realized by performing both a TST and IGRA: see the algorithm (50) in figure 3. A positive result with either TST or IGRA should be considered evidence of TB infection. In children below 5 years of age, BCG status is not taken into account in order to maximize sensitivity.

The sensitivity of IGRAs for detecting TB infection in childhood is generally similar to TST, according to recent meta-analysis (47) (48) (51). The IGRAs specificity seems to be higher than TST and it explains the IGRAs advantage over TST in identifying a MTB infection in settings with high non-tuberculous mycobacteria (NTM) exposure or high BCG vaccination coverage. However, there are insufficient data to strongly recommend an IGRA as the first diagnostic test in children below the age of 5 years (and particularly among children below the age of 2 years) (52) (53). In Belgium, the choice of test in children below the age of 5 years will be an individual decision based on the algorithm.



* See: 3.3.5.d. Situations in which TST and IGRA can be used consecutively to increase specificity

Figure 3. Algorithm for the use of TST and IGRA in children. Entry into the algorithm assumes that the child has at least 1 risk factor for TB (based on reference 49)

3.3.3. LTBI testing during pregnancy

Both TST and IGRA may be used. Results of both tests do not appear to be altered by pregnancy, nor do they pose any danger to the unborn child (30).

3.3.4. LTBI testing in PLHIV

Screening for LTBI should be made using a two-step approach (see figure 4):
- initial screening by TST. An induration of ≥ 5 mm in diameter is considered positive;
- if TST is negative, perform IGRA within 72 hours of tuberculin injection to avoid false positivity of the IGRA (54).

For organizational reasons, it may be more practical to perform TST and IGRA simultaneously.

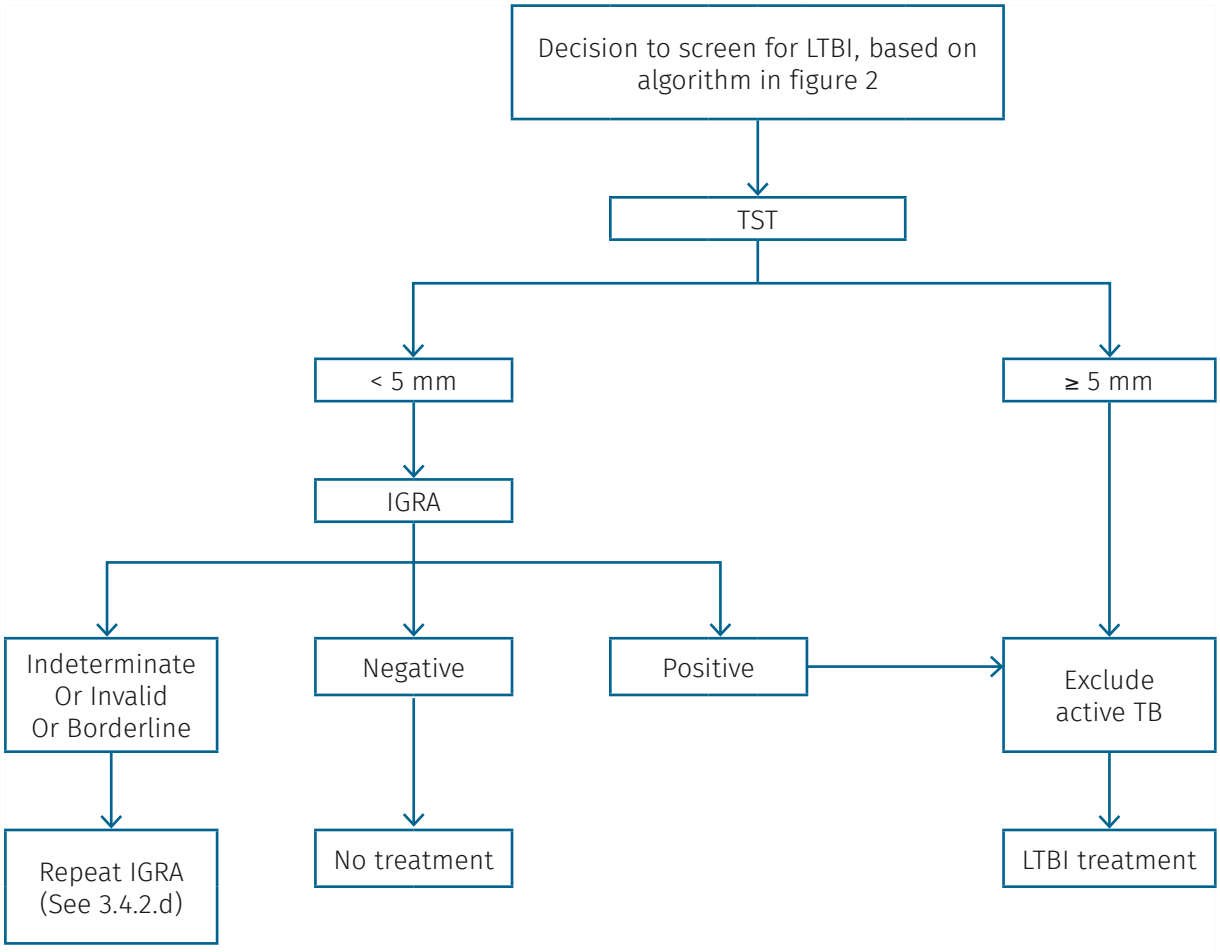


Figure 4. How to screen for LTBI in PLHIV (based on reference 24)

3.3.5. Summary: TST or IGRA? Or both?

3.3.5.a. Situations in which TST is preferred

TST is recommended in cases of continuous exposure to MTB, for instance in the context of occupational exposure in health care workers, personnel of detention centres or asylum seekers centres. Ideally, at baseline (e.g., at hiring), two tests should be done with a 1 to 2-week window period to allow boosting (see 3.4.1.h). The result of the second test is the one to be taken into consideration. TST can be repeated over time if the test remains negative. IGRA has shown to have too many reversions/conversions and thus is less useful in this context (54).
In children below the age of 5, the TST is to be preferred, given the inconsistent results with respect to IGRA sensitivity in this age group. IGRAs perform well in children aged 5 years or older.

PERIODIC TESTING

Recommended for persons with continuous exposure to MTB.

For periodic testing, TST is recommended. If the initial TST is positive, or if the TST becomes positive at a certain moment, it is not useful to continue the periodic testing. If a risk event occurs (contact with infectious case, developing a condition that increases the risk of TB), the person needs to be evaluated clinically and radiologically and instructed/informed on the need for another evaluation if signs and symptoms appear.

IGRA is not recommended for periodic testing. If the initial testing was done by IGRA nevertheless, the test should not be repeated periodically (see 3.4.2.h and 3.4.2.i). IGRA should only be repeated if a risk event occurs.

3.3.5.b. Situations in which IGRA is preferred

An IGRA will be useful in situations where the TST could show a false positive result because of earlier BCG vaccination. The following individuals should preferably be tested by IGRA:
- vaccinated with BCG in the course of the previous 12 months (except children < 5 years of age: BCG is not taken into account, see algorithm in 3.3.2);
- having received repeated BCG-vaccinations;
- BCG administered when older than 1 year of age;
- children 5 years or older who have received BCG vaccine; or who are unlikely to return for the TST reading (see algorithm in 3.3.2).

3.3.5.c. Situations in which TST and IGRA can be used consecutively to increase sensitivity

We recommend TST first, followed by IGRA if TST is negative. If TST is done first, IGRA should be done within 72 hours to avoid false positivity of the IGRA (55). It is also possible to do TST and IGRA simultaneously.

The two-step approach will be useful for:
- persons with immunodepression, such as HIV-infected individuals (see 3.3.4), dialysis patients and individuals undergoing immunosuppressive therapies;
- children with a negative TST result who present a high clinical suspicion for TB disease or a high risk for infection, progression or poor outcome (see 3.3.2).

3.3.5.d. Situations in which TST and IGRA can be used consecutively to increase specificity

If the TST is positive but the likelihood of a MTB infection is doubtful, an IGRA can be used to exclude a false positive result. This could be the case if the person has been exposed to NTM or has received a BCG vaccination. Two-step testing may also be useful in children with a positive TST result if the child is healthy and at low risk or if additional evidence is needed to ensure adherence (see 3.3.2). Since a positive IGRA result provides additional evidence of infection, this may help the physician to motivate the patient or the parents of a child to accept LTBI treatment and adhere to it.

IGRA should be done within 72 hours to avoid false positivity of the IGRA (55), or both tests can be done simultaneously.

3.4. HOW TO INTERPRET TST AND IGRA TEST RESULTS

3.4.1. Interpretation of TST

3.4.1.a. Risk stratification

The TST result must be measured and recorded in millimetres (if no induration, record as 0 mm). It cannot simply be read as positive or negative. Its interpretation will be a trade-off between sensitivity and specificity. Although larger indurations are more likely to be the result of a TB infection, the TST results should be interpreted using risk-stratification cut-offs, considering TB prevalence, BCG vaccination status, immunological status, medical history, screening context and age. In a person at high risk of developing TB (e.g. PLHIV or other immunocompromised host), a smaller diameter of induration should be considered as positive.

The interpretation of the TST is to be made separately for adults (table 4a) and children (table 4b).

Table 4a. General criteria for the interpretation of a TST in adults

Induration diameter	Interpretation	
< 5 mm	Negative	
≥ 5 mm	Positive	• HIV-infected individuals (independent of $CD4^+$ count and antiretroviral therapy status) • Severe immunodepression, such as solid organ transplant recipients, end stage renal deficiency with or without dialysis, immunosuppressive treatments (e.g. anti-TNFα treatment)
5-9 mm	Doubtful	• Individuals with a recent contact with a contagious case of TB • Persons aged ≥ 65 years
≥ 10 mm	Positive	• Direct exposure to an infectious TB patient • Individuals at risk of developing active TB (see table 1 in 3.1.1) • Individuals belonging to a group with an increased risk of exposure to TB (see 3.1.2) (56)
10-14 mm	Doubtful	• When the individual does not present any of the risk factors • Individuals vaccinated with BCG in the course of the previous 12 months • Individuals having received repeated BCG-vaccinations • Individuals vaccinated with BCG over the age of 1 year
≥ 15 mm	Positive	

Table 4b. General criteria for the interpretation of a TST in children

Induration diameter	Interpretation	
< 5 mm	Negative	
≥ 5 mm	Positive	• Children with a recent contact with a contagious case of TB • Children with immunodepressive conditions, including HIV infection • Children receiving immunosuppressive therapy, including anti-TNFα treatment or immunosuppressive doses of corticosteroids
≥ 10 mm	Positive	• Children younger than 5 years of age presenting none of the risks mentioned above • Children presenting a high risk for the development of active TB: medical conditions such as Hodgkin disease, lymphoma, diabetes mellitus, chronic renal failure or malnutrition • Children presenting a high risk of exposure to active TB: – born, or parents born, in high-prevalence region; – traveling to high-prevalence region (born… and travelling… sont des sub-bullet points de children…)
≥ 15 mm	Positive	

3.4.1.b. Negative screening results in contacts

A negative LTBI test result obtained less than 8 weeks after exposure is considered unreliable for excluding infection after a recent contact. Following infection with MTB, there is an ante-allergic phase which takes 2 to 12 weeks, with a median of 6-8 weeks. Nevertheless, LTBI testing should not be postponed because non-reactivity during the ante-allergic phase reflects the person's status prior to the contact and will be useful as a baseline when retesting is done after the ante-allergic phase.

- In the case of normal immunity, the test must be repeated 8 to 12 weeks after last contact with the index case (25) in order to overstep the ante-allergic phase.
- In the case of HIV infection, two-step testing is to be envisaged from the start (see 3.3.5.c). Repeat testing after 8 weeks is not indicated. Preventive therapy will be initiated regardless of the test result (see 4.1.2.b) but this test result is to be kept in the patient's file as a baseline reference for possible future testing.

If the initial test is performed more than 8 weeks after exposure, there is no need to repeat the test if there is no notion of immunodepression. In case of primary or acquired immunodeficiency: perform two-step testing (57) (see 3.3.5.c).
The possibility of a false negative result should always be considered.

3.4.1.c. Doubtful TST results

- Consider performing IGRA test. This needs to be done within 72 hours of the TST. The most practical approach would be to have everything needed for the IGRA ready at the time when the TST is read. If an IGRA can be performed, its result can be considered the final one, but the interpretation of a negative IGRA following a doubtful TST will depend on the risk of developing active disease if infected with MTB (see table 8 in 4.1.1.b).

- If the IGRA cannot be realised within 72 hours, it will be necessary to wait 3 months in order to allow the amplification effect of the ESAT-6 and CFP-10 antigens in the TST to wane.

- If no IGRA can be performed and no active TB is clinically suspected, repeat the TST 8 to 12 weeks later. In case this repeated testing is negative, NTM infection was likely. If the variation is less than or equal to 3 mm, this might be due to technical variability. If the variation is equal to or more than 10 mm, consider as a conversion to positive test requiring follow-up and LTBI treatment. A TST diameter variation between 4-9 mm does not allow to reach a definitive conclusion. In such a case, it is recommended to ask the advice of an expert.

- In children, no "doubtful" category is recognized because in children one wants to obtain maximum sensitivity.

3.4.1.d. False positive TST results

It is important to note that exposure to NTM or prior vaccination with BCG can lead to false positive TST.

- The absolute impact of NTM is surprisingly low, even in populations with a high prevalence of NTM. The relative occurrence of NTM compared with TB is greater in low TB incidence countries but remains < 5 % (58). In a meta-analysis including 12 studies and over 1 million individuals, the frequency of false positive TST due to NTM was < 3 % for TST of > 10 mm. NTM reactions will, therefore, be relevant only if the likelihood of true TB infection is very low. In one review, the absolute prevalence of false positive TST because of NTM ranged from 0.1 % in Montreal or France to a maximum of 2.3 % in India (58).

- BCG can be a possible source of a false positive TST. The probability that a TST reaction resulted from TB infection – and not from BCG vaccination – increases if at least one of the following is present:
  - the size of induration increases;
  - the individual has been in contact with an infectious index case;
  - the individual belongs to a high risk group for TB;
  - the individual originates from a country with a high TB prevalence;
  - the length of time between vaccination and TST increases.

  In HIV-infected patients, there is evidence showing that the loss of BCG-induced TST reactivity may be greater than the loss of *M. tuberculosis*-induced TST reactivity in the course of HIV-infection, leading to fewer false positive TST results in these patients (59).

  In countries where the burden of disease is low and the children are mainly NOT immunized with BCG, it is recommended that the interpretation of the TST should be identical both in children who have and who have not received a BCG vaccination (60).

- The injection of a dose of tuberculin exceeding the recommended dose (0.1 ml), an inexperienced or biased reader or an error in recording can also be the cause of a false positive TST.

3.4.1.e. False negative TST results

False negative results can have two main causes: technical (suboptimal execution) and biological, as shown in table 5.

Table 5. Causes of false negative TST

Technical (correctable)	
Tuberculin material	• Improper storage (exposure to light for more than 24 hours above 8°C) • Contamination, improper dilution, or chemical denaturation
Administration	• Injection of too little tuberculin, or too deep (should be intradermal) • TST within 2 to 12 weeks following TB exposure (ante-allergic phase)
Reading	• Inexperienced or biased reader • Error in recording
Biological (not correctable)	
Infections	• Active TB (especially if advanced, such as life-threatening meningitis or disseminated disease in children) • Other bacterial infection (typhoid fever, brucellosis, typhus, leprosy, pertussis) • HIV infection (especially if $CD4^+$ count < 200) • Other concurrent or recent viral infection (influenza, measles, mumps, varicella) • Fungal infection (South American blastomycosis)
Recent live virus vaccination	• Measles, mumps, rubella, polio, varicella, yellow fever and live-attenuated influenza (the inactivated influenza vaccine commonly used in Belgium has no influence on the TST result). → Following vaccination, one needs to wait at least 6 weeks before doing the TST (61).
Immunosuppressive drugs	• High dose corticosteroids, TNFα inhibitors, anti-CD52, anti-CD20 and other similar drugs
Metabolic diseases	• Uncontrolled diabetes, chronic renal failure, severe malnutrition, stress (surgery, burns)
Diseases of lymphoid organs	• Lymphoma, chronic lymphocytic leukemia, sarcoidosis
Age	• Children < 6 months; elderly (≥ 65 years)

3.4.1.f. Conversion of TST

Conversion of a TST can only be established under the following conditions: the individual goes from a negative test to a positive test during a period of fewer than two years and the difference between the indurations of the two tests is at least 10 mm when the same dose and type of tuberculin is used in both assays. Conversion occurs in the following 2 situations:

- an initial negative test is followed by a positive test in the 2 to 12 weeks following contact with a contagious index case;
- in the context of a negative TST becoming positive after serial testing.

Conversion of the TST is evidence of a recent exposure leading to infection, which implies a major risk for the development of active TB.

3.4.1.g. Reversion of TST

When a positive TST is followed by a negative test, this is probably due to a change in immunity. The reaction to the tuberculin can be reduced following a decrease in immunity related to age or illness or following immunosuppressive therapies.

In the case of serial testing changes in induration may occur, yet the cause remains unknown.

It should be noted that a false positive TST of ≥ 10 mm occurring after exposure to NTM or BCG may diminish more quickly than in actual LTBI.

3.4.1.h. Booster effect of TST

Some people infected with MTB may have a negative reaction to the TST if many years have passed since they became infected and their cell-mediated immune response has waned. They may have a positive response to a subsequent TST because the initial test has stimulated their ability to react to the test, probably as a result from recall of waned cell-mediated immunity, akin to the anamnestic serologic response. This effect can also occur following infection with NTM or after vaccination with BCG (31). This is commonly referred to as the "booster phenomenon".

Boosting may incorrectly be interpreted as a skin test conversion (going from negative to positive in a period of less than two years). For this reason, repeating the TST can be considered at the time of initial testing for individuals who may be tested periodically (e.g., health care workers) or elderly persons at high risk of active TB disease. If the initial TST result in the context of periodic testing is positive, consider the person infected at baseline and evaluate and treat them accordingly. If the first test result is negative, the TST should be repeated in 2 weeks' time. If the second test result is positive, consider the person infected and evaluate and treat them accordingly; if both steps are negative, consider the person uninfected and classify the TST as negative at baseline testing.

The size of the induration of the second TST combined with the increase in induration compared to the first TST may help to distinguish boosting from conversion. For instance, boosting has been defined as a second reaction of ≥ 10 mm and an increase in induration of at least 6 mm, but alternate criteria have been suggested based on the prevalence of boosting in a particular population (62). In general, the larger the induration and the higher the increase, the more likely it will be a conversion.
The following considerations may also be of help:

- Boosting is maximal if the interval between the first and second test is between 1 and 5 weeks and is much less frequent if the interval is only 48 hours or more than 60 days, although boosting can be detected one or more years after a first negative tuberculin test.

- The incidence of boosting increases with age, due to immunoscenesence (63). Among geriatric patients in Belgium, the occurrence of waning was estimated at 24-34 % in the 65 to 74 age group and 39-56 % in the 75 to 84 age group (64). It is essential that all older persons (≥ 65 years) who undergo a TST be retested within 2 weeks after a negative response (induration of < 10 mm) is measured, to ensure that a potentially false-negative reaction is recognized.

- Boosting is more likely if testing was done in a context where there is no presumption of exposure.

The clinical context is important as well. If the benefits of LTBI treatment outweigh the risks (for instance if a person who needs to be treated with anti-TNFα, presents an increased TST reaction) the clinician will be more inclined towards conversion and start the LTBI treatment.

3.4.2. Interpretation of IGRA

Assessing the probability of LTBI requires a combination of epidemiological, historical, medical and diagnostic findings that should be taken into account when interpreting IGRA results.

3.4.2.a. Interpretation of the QuantiFERON®-TB Gold-Plus test (QFT®-Plus)

The laboratory performs an ELISA assay to measure the IFN-γ levels (IU/ml) in each tube of the QFT®-Plus test (see annex A3.2). Making use of software provided by the QFT®-Plus manufacturer, the laboratory will arrive at a result of *Positive*, *Negative* or *Indeterminate* based on the measurements observed in the 4 tubes (see table A2 in annex A3.2). If the result is *Indeterminate*, the test should be repeated unless there is doubt about the immune status of the patient. In such case, a low lymphocyte count should be excluded first.

If the result is given as *Positive* or *Negative*, this should be interpreted with caution. Similar to the TST, which has a zone of doubtful results, there is a grey or borderline zone (65) around the cut-off point of 0.35 IU/ml used by the QFT®-Plus software. For this reason, the laboratory should always communicate the values observed in the 2 test tubes TB1 and TB2. These values can be interpreted based on table 6.

Table 6. Interpretation of valid QFT®-Plus test results

	Value observed in either TB1 or TB2				
	< 0.2	0.2 – 0.35	0.35	0.35-0.7	> 0.7
Interpretation	Negative	Borderline negative	Cut-off	Borderline positive	positive

It is recommended to repeat the test in case of a *borderline positive* or *borderline negative* result.

3.4.2.b. Interpretation of T-SPOT®.TB test

In the laboratory, the number of "spots" (IFN-γ producing cells) are counted in 4 wells (see annex A3.3). If the counts in the Nil Control or in the Positive Control indicate an *Invalid* result (see figure A1 in annex A3.3), a new sample should be collected and tested. A valid result needs to be interpreted by looking at the difference observed between the counts observed in the Panel A and Panel B wells and the Nil Control. The test result will be given as *Positive*, *Borderline* or *Negative*, according to table 7.

Table 7. Interpretation of valid T-SPOT®.TB test results

Panel A minus Nil	Panel B minus Nil		Interpretation
One or both have ≥ 8 spots		→	Positive
Highest count in either one is 5, 6 or 7 spots		→	Borderline
Both have ≤ 4 spots		→	Negative

In case of a *Borderline* result, a new sample should be collected and tested.

3.4.2.c. Negative screening results in contacts

- If the initial test is performed less than 8 weeks after known exposure: repeat the test 8 to 12 weeks after last contact to overcome the ante-allergic phase. In case of immunodeficiency, repeat testing is not indicated, and preventive therapy will be initiated regardless of the test result.
- If the initial test is performed more than 8 weeks after exposure: no need to repeat the test if there is no notion of immunodepression. In the case of immunodeficiency, consider repeating the test on a case by case basis, preferably when immunosuppression might be at the lowest.

DISTINCTION BETWEEN *INDETERMINATE*, *INVALID* AND *BORDERLINE* RESULTS OF IGRA TESTS

If the test results do not allow to draw a conclusion, the laboratory will enter the result as *Indeterminate* if QFT®-Plus test (see annex A3.2.3) or *Invalid* if T-SPOT®.TB test (see annex A3.3).

Borderline is an interpretation, made by the clinician, based on the valid results of the test as communicated by the laboratory (see tables 6 and 7).

3.4.2.d. Indeterminate, invalid and borderline IGRA results

If the result of the QFT®-Plus test is *Indeterminate*, the test should be repeated unless there is doubt about the immune status of the patient. In such case, a low lymphocyte count should be excluded first.

If the T-SPOT®.TB test indicates an *Invalid* result, a new sample should be collected and tested.

If the result of either the QFT®-Plus test or the T-SPOT®.TB test is interpreted as *Borderline*, consider repeating the IGRA test after 8 weeks (to ensure that a potential ante-allergic phase has been overcome).

If the second test still does not give a clear-cut result, all required clinical investigations need to be done to exclude TB. Referral to a specialist may be warranted. As long as no decision has been made, careful follow-up remains necessary and the person must receive all relevant information about when to seek medical attention.

3.4.2.e. False positive IGRA results

- Four NTM (*Mycobacterium marinum*, *kansasii*, *szulgai* and *flavescens*) contain the genes encoding ESAT-6 and CFP-10 and can result in false positive results.
- Both immunological and technical phenomena can affect the reproducibility of IGRA and lead to false positive results.

3.4.2.f. False negative IGRA results

- In cases with immunodepression such as HIV-infection and immunosuppressive therapies, the sensitivity of the IGRA can be reduced. Low $CD4^+$ counts are associated with less clear-cut IGRA results, and in this case the test should be repeated to distinguish technical issues from true anergy.
- The sensitivity of IGRA can also be affected by anergy due to active TB.
- Both immunological and technical phenomena (65) can affect the reproducibility of IGRA and lead to false negative results.
- Apart from measles, the effect of live-virus vaccines on IGRA results has not yet been studied but, in theory, it could be similar to their effect on the TST results. In the absence of data, the same spacing as recommended between measles vaccination and TST or IGRA should be applied to all live-virus vaccines. This means waiting at least 6 weeks after vaccination before testing (61).

3.4.2.g. Booster effect of IGRA

- No booster effect exists following previous IGRA testing.
- The IGRA result can be amplified by a previous TST, as ESAT-6 and CFP-10 are included in tuberculin (66). This amplification appears after 72 hours and disappears within three months (66). It is recommended to perform the IGRA within the first 72 hours following the administration of TST. If an IGRA done more than 72 hours after the TST shows a negative result, this can be considered to reflect the true situation. If the IGRA is positive, however, it cannot be known if it is a true positive result or the effect of the TST. To be certain, it will be necessary to repeat the IGRA 3 months after the TST.

3.4.2.h. Conversions and reversions of IGRA

- Conversions and reversions can occur for repeated IGRAs, even more frequently compared to TST. There is no clearly established cut-off to distinguish between true conversions/reversions and variations due to immunological state or technical variations, which complicates the interpretation of repeated IGRAs variability.
- Reversions occur most frequently when the values of the previous test were just above the cut-off or in cases of discordant results (TST– / IGRA+).
- The time until IGRA conversion remains unknown. Most likely, the ante-allergic period will be similar to the TST one, and most conversions will occur within 8 to 12 weeks after contact. However, conversions have been described > 3 months after contact.
- Because of the variability of repeated IGRA, serial testing is not recommended. It will be important to ensure proper clinical follow-up.

3.4.2.i. Reproducibility of IGRA tests

Despite a highly standardized technique, the variability of IGRA may lead to false positive and negative results. IGRA variability can have different causes, including pre-analytical factors (collection and transportation of the blood sample), technical issues and the amount of blood present in the tubes, intra- and interlaboratory variations and intra-individual variations (65).

4. TREATMENT OF LATENT TUBERCULOSIS INFECTION

4.1. WHO SHOULD BE TREATED FOR LTBI

4.1.1. General approach

4.1.1.a. Positive LTBI testing result = LTBI treatment

Certain groups, listed in 3.1.1, are at (very) high risk of developing TB disease once infected and need to be tested for LTBI. If either the TST or the IGRA is positive, LTBI treatment should be envisaged. Treatment of LTBI is essential to controlling and eliminating TB because it substantially reduces the risk that TB infection will progress to TB disease. Currently available regimens for the treatment of LTBI have an efficacy ranging from 60 % to 90 %, the protection of which can last up to 19 years in low endemic countries, such as Belgium (13). If the treatment recommendations outlined in 4.2 are adhered to, the WHO states unequivocally that the benefits of all the treatment options outweigh the potential harm (5).

4.1.1.b. Discordant results between TST and IGRA

The use of both a TST and an IGRA in LTBI screening is limited to specific situations and often leads to discordant results (67). Either IGRA is applied in the context of a doubtful TST (see 3.4.1.c), or two-step testing is used to increase screening sensitivity or specificity. Nevertheless, if both tests have been applied and discordant results are found (see table 8), consider:

a. Clinical workup including medical history to guide the interpretation of the results.
b. In cases where the medical history does not include recent BCG vaccination, and either test is positive, treatment for LTBI should be considered if the risk to develop TB is high (e.g., immunodepression, recent contact...). In BCG vaccinated individuals, evaluate the possibility of a false positive TST result based on the considerations in 3.4.1.d.

Table 8. Guidance for the interpretation of LTBI testing when both results for TST and IGRA are available (68).

	Risk of developing active disease if infected with MTB						
	High (see table 1)			Low			
	IGRA Positive	IGRA Negative	IGRA Borderline	IGRA Positive	IGRA Negative		IGRA Borderline
					Adults	Children	
TST Positive	Consider treatment for LTBI			Consider treatment for LTBI	Treatment for LTBI is not necessary	Consider NTM. Seek advice from specialist	Repeat IGRA test or base interpretation on TST result
TST Doubtful	Consider treatment for LTBI	Repeat TST	Consider treatment for LTBI	Consider treatment for LTBI	Treatment for LTBI is not necessary		Repeat IGRA
TST Negative	Consider treatment for LTBI	Treatment for LTBI is not needed except in immuno-depressed contacts	Repeat IGRA test or base interpretation on TST result	Consult a TB specialist to consider treatment for LTBI	Treatment for LTBI is not necessary		

4.1.2. Approach in specific situations

4.1.2.a. Children (2) (9) (69)

- Since children with a positive LTBI test have been recently infected, it is essential for them to receive LTBI treatment (see table 2 in 3.1.1).

- A child, aged less than 5 years and exposed to a case of pulmonary TB but with a negative LTBI test result should receive "window prophylaxis", after an appropriate clinical evaluation (i.e. history, symptoms, radiological and microbiological exams if needed) has excluded active TB. Eight to 12 weeks after the most recent exposure, the child should be retested. In children below six months of age, however, retesting should be postponed until the child has reached the age of 6 months. If, following the second test, LTBI is excluded, "window prophylaxis" can be stopped.

- In immunocompromised children, a full course of LTBI treatment is initiated right away, irrespective of the LTBI test result. No second test is required.

Window prophylaxis is the practice of treating LTBI negative contacts of TB cases with preventive therapy during the early phase when the LTBI test may not yet be positive. Window prophylaxis prevents rapid progression to active TB soon after infection.

4.1.2.b. People living with HIV

- If testing positive for LTBI: give LTBI treatment.
- If testing negative for LTBI: no need to provide LTBI treatment unless the PLHIV is a contact of a contagious TB case (see 3.1.4.c). A full course of LTBI treatment is to be given, without repeating the LTBI testing after 2 months.
- If testing results are discordant: envisage LTBI treatment if one of the tests is positive and another high risk for TB is present (see table 1).

4.1.2.c. Pregnancy, postpartum and lactation

- Pregnancy does not influence the pathogenesis of TB or the risk of progression towards active TB after exposure, and it does not affect the response to treatment (70) (71). However, during pregnancy and the 3 months' postpartum, there may be a higher risk for hepatotoxicity due to INH. Delaying the LTBI treatment is preferred (30)
- Consider immediate treatment for LTBI if the woman is HIV infected or has a recent contact and monitor after TB disease is excluded. If there are no risk factors (e.g. immunodeficiency or HIV) for the progression towards TB, LTBI treatment is to be delayed until 3 months following delivery.
- When treatment was started before the pregnancy, treatment should be continued (72).
- Breastfeeding is not contraindicated in women taking (non-MDR) LTBI treatment.
- Approximately 3 % of the INH maternal dose is secreted in the breastmilk. The amount of INH in breast milk is inadequate for treatment of children with LTBI.

4.1.2.d. Presence of fibrotic lesions on chest X-ray

As with other forms of LTBI, the benefit of treatment for LTBI must be weighed against the risk of drug toxicity, non-adherence and the possibility that the fibrotic lesions may be active TB. The lifetime risk of reactivation can be stratified by age and, if available, TST diameter (with diameter ≥ 15 mm indicating a high probability of reactivation) (36). In general, younger age indicates a higher risk of reactivation and active TB should be excluded. If no active TB is detected, start LTBI treatment. With increasing age, the risk of reactivation lowers, but the probability of adverse drug effects increases. The treating physician should weigh the risk of LTBI treatment against the extent of the lesions.

4.1.3. Special situation: preventive treatment for contacts of multidrug-resistant tuberculosis cases

Before making any decision regarding preventive therapy in contacts of MDR-TB cases presumed to be infectious, expert advice must be sought. There is sparse evidence on the effectiveness and safety of using anti-TB drugs to prevent active TB among infected adult and childhood contacts of MDR-TB cases. Furthermore, determination of the drug susceptibility profile for drugs to be used as preventive treatment for MDR contacts poses both technical and logistic challenges. In addition, the drugs used for MDR-TB may lead to drug-related harms, which would necessitate additional cost for close monitoring.

All contacts have to be tested for LTBI.

- Children < 5 years of age and immunocompromised individuals of all ages with a positive LTBI test result should receive preventive therapy, after excluding active TB, for a duration of 6 months.

- Based on expert opinion (73) all other contacts of any age with a positive LTBI test result could be offered preventive therapy, after excluding active TB, for a duration of 6 months (74). If treatment is not initiated because it is refused or there are contra-indications or doubts about treatment compliance, regular clinical and radiological monitoring during 2 years is indicated, every 2-3 months during the first 6 months, and every 6 months thereafter.

- If the LTBI test is negative, window prophylaxis should be prescribed to very young children and HIV-infected individuals with very intimate and prolonged contact with MDR-TB patients likely to be contagious (smear-positive, coughing source case with cavitary disease, or occurrence of TST conversions among other contacts indicating transmission of TB). A second LTBI test is to be performed 8 to 12 weeks after the date of last exposure. If it is positive, preventive therapy is to be continued for a total duration of 6 months. If the repeat test is negative, window prophylaxis can be stopped but not before 12 weeks after the date of last exposure.

The preventive therapy regimen will consist of 2 drugs. The choice of drugs will be determined based on the DST results of the index case:

- If the strain is susceptible to the fluoroquinolones, the first drug in the regimen should be moxifloxacin or levofloxacin. The second drug should preferably be ethambutol (75) (but in young children this should not be the first choice) or prothionamide. If this is not an option, another drug is to be selected based on the DST results of the index case (76), but pyrazinamide is to be avoided because its combination with a fluoroquinolone has been shown to be associated with more frequent adverse events (77).

- If the DST of the index case indicates that the strain is resistant to the fluoroquinolones, a consilium of MDR-TB experts must give advice.

4.2. TREATMENT REGIMENS FOR LTBI

4.2.1. General considerations

Several possible treatment regimens are available. In Belgium, the main options are isoniazid (INH) monotherapy, rifampicin (RMP) monotherapy and a combination of INH + RMP. The combination of INH + rifapentin, a rifamycin with a serum half-life five times that of RMP, thus permitting weekly dosing, is not envisaged because rifapentin is not available on the Belgian market. The combination of RMP and PZA has been abandoned in the face of the higher hepatotoxicity (78) (79) (80).

A 2014 meta-analysis (81) observed that relatively few direct comparisons between regimens were reported and some studies only provided sparse data, particularly for current regimens. No study showed the superiority of one regimen over any other. Regarding safety, fewer hepatotoxicity events were reported for 3 to 4 months' RMP regimens compared to 6- and 9-months' INH regimens. However, the level of evidence remains low. Thus, there is no current recommendation to preferably choose a regimen of RMP over INH in patients at higher risk of hepatotoxicity.

The 2018 LTBI Guidelines of the WHO (5) state that 6 months' daily monotherapy with INH is the standard treatment for both adults and children living in countries with either high or low TB incidence, including for people living with HIV.

The WHO conditionally recommends that people living with HIV may profit from continuous administration of INH during 36 months, particularly if they have a positive TST (82), but only in appropriate settings with high TB prevalence and transmission.

A combination of daily INH and RMP for 3 months or daily RMP monotherapy for 4 months may be a good alternative if levels of RMP resistance are low in the country. The efficacy and safety of these regimens are similar to those of INH monotherapy (83) (84). Shorter regimens have also been shown to be significantly associated with increased adherence to treatment.

In children, the 6-months' INH regimen is highly efficacious in clinical trials, but its effectiveness is limited by poor adherence and low completion rates. Treatment regimens using 4 months of daily RMP (85) or 3 months of daily INH and RMP (86) are safe and have significantly higher completion rates. If breastfed children or adolescents are treated with INH containing regimens, supplementation with pyridoxine (vitamin B6) 2 mg/kg/day is recommended.

During pregnancy and lactation, INH daily during six months is the preferred regimen. Supplementation with pyridoxine (vitamin B6) 250 mg/week is recommended.

Because of its interaction with oral contraceptives, RMP should not be the drug of choice when prescribing LTBI treatment to women on the pill.

When a person is known to be exposed to an infectious person with an INH-resistant strain or is intolerant to INH, a course of treatment using RMP is recommended.

In HIV-infected individuals, RMP containing regimens should be used with caution being treated with certain antiretroviral medications. If it is not possible to prescribe an INH based regimen, for instance when the strain of the index case is INH resistant, seek expert advice concerning the possibility of an alternative cART regimen.

4.2.2. LTBI treatment regimens recommended in Belgium

When selecting appropriate treatment options, the clinicians should consider the characteristics of the patients who are to receive LTBI treatment to ensure that it is not only initiated but also completed. All of the proposed regimens can be self-administered. Directly observed therapy (DOT) may help to improve compliance, but the effort, time and cost involved must be carefully weighed against the expected benefit.

The LTBI treatment regimens recommended in Belgium are shown in table 9.

Table 9. LTBI treatment regimens recommended in Belgium

Regimen	Indication
6H (INH daily during 6 months)	standard recommended regimen in Belgium
3RH (daily RMP and INH during 3 months)	children < 2 years of age [5]
	} valid alternative if compliance is a concern, particularly in children
4R (RMP daily during 4 months)	
	if the strain of the index case is known to be INH resistant

One important constraint to take into account is that RMP, when prescribed for the treatment of LTBI, is not reimbursed in Belgium. BELTA-TBnet may cover the cost in certain conditions. Further explanations regarding the project as well as contact information can be found at www.belta.be.

Table 10 gives the recommended doses of INH and RMP. These drugs are commercially available in Belgium under the names of Nicotibine® (isoniazid) and Rifadine® (rifampicin). Further information regarding these drugs can be found on the website of the Belgian Centre for Pharmacotherapeutic Information (BCFI/CBIP) [6] under 11.1.8.1 (isoniazid) and 11.1.8.2 (rifampicin).

5 This recommendation is based on the following considerations:
- Better compliance because of shorter duration
- Best alternative in the absence of rifapentin availability
- Often, it is not known at the time of starting window prophylaxis whether the index case has an INH resistant strain. This is particularly important in younger children who are at risk of developing more severe forms of TB.

6 http://www.bcfi.be/nl/chapters/12?frag=10355&trade_family=23382 (Flemish)
http://www.cbip.be/fr/chapters/12?frag=10355&trade_family=23382 (French)

Table 10. Recommended treatment dosing

Drug	Dose per body weight		Maximum dose
	Child	Adult	
Daily INH	10 mg/kg (range 7-15 mg)	5 mg/kg	300 mg
Daily RMP	15 mg/kg (range 10-20 mg)	10 mg/kg	600 mg

Dosages are the same for both mono- and bi-therapy.
In children, dosing must be adapted regularly according to changing weight. Magistral preparations in capsules are preferred over syrups.

4.3. BEFORE STARTING LTBI TREATMENT

Before starting any treatment for LTBI, active TB [7] must be excluded, particularly if fibrotic lesions are seen on the chest X-ray. A clinical workup, including clinical assessment of symptoms and signs of active TB (i.e. hemoptysis, cough, fever, night sweats or weight loss), chest X-ray and, when indicated, additional radiological and microbiological tests, should be performed to rule out active (pulmonary or extra-pulmonary) TB. It is important that this testing is done before any treatment for LTBI is initiated, to avoid development of resistance in a patient that might have active TB. If these exams do not show active TB, LTBI treatment can be initiated if the patient will adhere to treatment and the risk of developing active TB outweighs the risk of LTBI drugs. If the treating physician has doubts about the adherence of the individual, the risk and benefit of therapy must be weighed against the risk of emerging resistance if active TB would develop during inadequate LTBI treatment (4). A risk analysis evaluating the likelihood of non-compliance should be performed. If the patient is considered to present a high risk for developing TB but there are doubts about the patient's compliance, a short regimen under strict DOT should be envisaged.

Contra-indications to the LTBI treatment must be excluded, such as hypersensitivity to the treatment regimen and severe hepatic failure. Baseline laboratory testing for measurements of serum aspartate aminotransferase, alanine aminotransferase and bilirubin is only recommended for those with:

- a history of liver disease;
- regular use of alcohol;
- intravenous drug use;
- chronic liver disease;
- HIV infection;
- aged more than 35 years (87);
- pregnancy or the immediate postpartum period (i.e., within 3 months of delivery).

For individuals with abnormal baseline test results, routine periodic laboratory testing should be carried out depending on the physicians' judgement (e.g. monthly at the start of treatment).
Before starting INH based treatment, it is prudent to check the remaining G6PD activity if a possible G6PD deficiency is a concern (88).
If the drug sensitivity testing result of the index case is known, check whether the strain is susceptible to INH and RMP.

7 Diagnosis and treatment of tuberculosis in Belgium. Recommendations for physicians.
http://www.belta.be/images/stories/Aanb_diag_%20behand_TB2010.pdf (Flemish)
http://www.belta.be/images/stories/Reco_diag_trait_TBC2010.pdf (French)

4.4. FOLLOW-UP DURING TREATMENT

4.4.1. Routine monitoring

Regular clinical monitoring of individuals receiving treatment for LTBI through a monthly visit to health care providers is of critical importance to exclude active TB, ensure therapeutic compliance and detect adverse drug reactions.

The prescribing health care provider should explain the rationale of therapy and emphasize the importance of completing it. Those receiving treatment should be educated to contact their health care providers should they develop symptoms such as paraesthesia, anorexia, nausea, vomiting, abdominal discomfort, persistent fatigue or weakness, dark coloured urine, pale stools or jaundice.

The clinician as well needs to be on the lookout for drug side effects such as neurotoxicity and hepatotoxicity, while clinical evaluation is also necessary to exclude the development of active TB disease during LTBI treatment if suggestive symptoms develop.

Monthly blood draw is suggested for follow-up of hepatotoxicity in those with elevated liver tests from onset, chronic liver disease, HIV, pregnancy or postpartum, alcohol abuse and IV drug use. In children, the risk of INH-related hepatitis is minimal. Routine monitoring of serum liver enzymes is not necessary unless the child has risk factors for hepatotoxicity.

4.4.2. Ensuring adherence to treatment

Completion rates vary widely (from 6 % to 94 %) according to risk groups. In general, completion rates were lower among prisoners and immigrants compared with persons living with HIV and contacts; they were inversely proportional related to the duration of treatment (3) (89).

Determinants of treatment initiation, adherence and completion identified in a systematic review (89) were: 1) adverse drug reactions, 2) longer duration of treatment, 3) legal status among immigrants, 4) long distance from health facility, 5) history of incarceration, 6) absence of perception of risk, 7) presence of stigma, 8) alcohol and drug use, 9) unemployment, and 10) time lag between diagnosis and treatment.

Evidence on the efficacy of interventions to improve treatment adherence and completion showed that shorter treatment duration was significantly associated with increased adherence. Significant increases in completion rates were demonstrated with peer support and coaching among adolescents and adults; nurse case management among the homeless; cultural case management among immigrants; and educational interventions among inmates.

The evidence regarding the most appropriate interventions to improve treatment adherence and completion is heterogeneous and inconclusive. Techniques that may improve adherence include: directly observed therapy if patient is at high risk (e.g., HIV-infected, young child, or TB contact), patient education and instructions in the patient's primary language at every visit, nurse

confidentiality, patient reminders such as pill box, calendar, or timer. Even economic incentives and linking a person to social services may increase adherence.

Patients who interrupt or fail to complete the course of LTBI treatment should be encouraged to complete the treatment. Whether the original regimen should be continued or a new course of treatment should be started, is shown in table 11. It will depend on the immune status of the patient, the timing of the interruption (during the initial 3 months of treatment or later), the duration of the interruption (more than 6 months or less than 6 months) and the quantity of doses lost: the cut-off point is the loss of at least one-third of the intended LTBI treatment regimen – for a regimen of 6 months' duration, this implies a lapse in treatment that lasted 2 or more consecutive months or intermittent interruptions in treatment that total 2 or more months.

Continuation of treatment means that the original regimen will be continued until completion of the full duration of the intended treatment administration. For instance: if a 6 months' INH regimen is interrupted for 5 weeks after 2 months, the patient needs to take the remaining 4 months. It is not necessary to extend the regimen.

Restarting treatment means that a new course of the initial regimen will be given. The duration of the new course will be identical to the length of the initial one. A prolonged regimen is not necessary. Before starting the new course of LTBI treatment, active TB must be excluded.

Table 11. Criteria to continue the initial regimen or to start a new regimen in case of interruption of the LTBI treatment

		Quantity of doses lost			
		< one-third	> one-third		
Immunodepressed, especially due to HIV infection		restart	restart		
Timing of the interruption	During the initial 3 months	continue	restart		
	After the initial 3 months	continue	Duration of interruption	< 6 months	continue
				> 6 months	restart

If a patient has failed three attempts to complete LTBI treatment, the effect of further efforts is likely to be minimal.

4.5. MANAGING SIDE EFFECTS

4.5.1. Isoniazid

4.5.1.a. Hepatotoxicity

Historically, the incidence of INH-induced asymptomatic hepatitis has been reported in up to 10–20 % patients and overt hepatitis in 1 % (2) (90) (91). The incidence is generally reported to be age-related, with those older than 35 years at increased risk. However, the lack of specific diagnostic criteria complicates comparisons across studies. The current American Thoracic Society/Centers for Disease Control and Prevention (ATS/CDC) recommendations are that routine blood testing of the liver function is indicated only if baseline transaminases are abnormal or if the patient is at risk of hepatic disease, defined as having the human immunodeficiency virus, chronic liver disease, being pregnant or during postpartum, excessive alcohol consumption or an active intravenous drug user (92).

It is recommended that INH be withheld if a patient's transaminase level exceeds 3 times the upper limit of normal if associated with symptoms or 5 times the upper limit of normal if the patient is asymptomatic.

In people who have experienced a treatment interruption because of drug-induced hepatotoxicity: consider stopping the LTBI treatment after a careful risk/benefit assessment. If continuation of LTBI treatment is the preferred option, investigate other causes of acute liver reactions and wait until aspartate or alanine transaminase levels fall below twice the upper limit of normal, bilirubin levels return to the normal range and hepatotoxic symptoms have resolved (2). However, the clinician must balance risk and benefits if LTBI treatment is deemed to be the cause of the hepatotoxicity. Treatment may be stopped if the risk of severe hepatotoxicity is considered unacceptably high, but preventive treatment based on rifampicin monotherapy would be a valid alternative (81).

4.5.1.b. Peripheral neuropathy

It occurs in less than 0.2 % of people taking INH at usual doses. It is dose-related and is more common in people with malnutrition and in the presence of other conditions associated with neuropathy such as diabetes, HIV, renal failure, and alcoholism; usually the reaction is preceded by numbness in feet and hands. The incidence is higher in "slow acetylators". Pyridoxine (vitamin B6) supplementation is recommended only in such conditions or to prevent neuropathy in pregnant or breastfeeding women, in children being breastfed and in adolescents (2) (70) (93) (94).

4.5.2. Rifampicin

Grade 3 or 4 hepatotoxic adverse events occurred in 0.3 % of persons taking RMP (83). Transient asymptomatic hyperbilirubinemia may occur in 0.6 % of persons taking RMP and is more likely when RMP is combined with INH.

Cutaneous reactions, such as pruritus (with or without a rash), may occur in 6 % of persons taking RMP. They are generally self-limited and may not be a true hypersensitivity; continued treatment may be possible. Rarely, rifamycins can be associated with hypersensitivity reactions, including hypotension, nephritis or thrombocytopenia, and manifested by symptoms such as fever, headache, dizziness/ light-headedness, musculoskeletal pain, petechiae, and pruritus.
Gastrointestinal symptoms such as nausea, anorexia, and abdominal pain are rarely severe enough to discontinue treatment.

Orange discoloration of body fluids is expected and harmless, but patients should be advised beforehand. Soft contact lenses and dentures may be permanently stained.

4.5.3. Drug interactions

RMP interacts with a wide variety of drugs through the P450 3A cytochrome metabolic pathway. Rifamycins are known to reduce concentrations of such diverse drugs as methadone, oral antidiabetics, anticoagulants, hormonal contraceptives, antiepileptics, antidepressants and antiretrovirals (95). This list is not exhaustive, and clinicians are urged to closely work together with pharmacists to actively look for drug-drug interactions. If a RMP-based regimen cannot be avoided in women taking oral contraceptives, alternative methods of contraception should be envisaged such as barrier methods (condom, diaphragm) or IUD. RMP is contraindicated, or should be used with caution, in HIV-infected individuals being treated with certain antiretroviral medications. If no INH-based regimen is possible, expert advice needs to be sought regarding the modification of the cART regimen.

INH is known to reduce the metabolism of anticonvulsants.

4.6. AFTER THE LTBI TREATMENT HAS ENDED

Patients should be counselled to contact their treating physician if possible symptoms of active TB develop, such as coughing, hemoptysis, fever, night sweats and unexplained weight loss.

Explain to the patient that a positive TST or IGRA may remain positive for life and that a repeat test is unnecessary. In the case of re-exposure, a new (latent) infection can always occur; previous exposure does not protect against re-infection. A consultation with an expert physician should be sought.

Regardless of whether the patient completes treatment for LTBI, serial or repeat chest radiographs are not required unless the patient develops signs or symptoms suggestive of TB disease.

ANNEXES

Annex 1.
Countries with TB incidence > 100/100,000 (WHO 2018 [8])

Country	Population (millions)	TB incidence rate per 100,000
Lesotho	2	665
South Africa	57	567
Philippines	105	554
Mozambique	30	551
Gabon	2	529
Democratic People's Republic of Korea	25	513
Timor-Leste	1	498
Marshall Islands	0.1	480
Papua New Guinea	8	432
Mongolia	3	428
Central African Republic	5	423
Namibia	3	423
Kiribati	0.1	413
Indonesia	264	379
Congo	5	376
Guinea-Bissau	2	374
Zambia	17	361
Angola	30	359
Myanmar	53	358
Cambodia	16	326
Democratic Republic of the Congo	81	322
Kenya	50	319
Liberia	5	308
eSwatini (former Swaziland)	1	308
Sierra Leone	8	301
Botswana	2	300
United Republic of Tanzania	57	269
Djibouti	1	269
Pakistan	197	267
Somalia	15	266
Madagascar	25	238

8 Based on: *Annex 1. The WHO global database*. In: WHO Global tuberculosis report 2018. Apart from minor shifts, the list is unlikely to change dramatically from one year to the next. If in doubt about a particular country, consult the most recent information at https://www.who.int/tb/data/en/

Country	Population (millions)	TB incidence rate per 100,000
Tuvalu	0.1	236
Bangladesh	165	221
Zimbabwe	17	221
Nigeria	191	219
India	1 339	204
Uganda	43	201
Cameroon	24	194
Equatorial Guinea	1	191
Afghanistan	35	189
Haiti	11	181
Guinea	13	176
Gambia	2	174
Kyrgyzstan	6	170
Lao People's Democratic Republic	7	168
Micronesia (Federated States of)	0.1	165
Ethiopia	105	164
Nepal	29	159
Thailand	69	156
Chad	15	154
Ghana	29	152
Côte d'Ivoire	24	148
South Sudan	13	146
Bhutan	0.8	134
Cabo Verde	0.5	134
Malawi	19	133
Viet Nam	96	129
Senegal	16	122
Sao Tome & Principe	0.2	118
Peru	32	116
Greenland	0.6	116
Burundi	11	114
Bolivia (Plurinational State of)	11	111
Palau	0.1	106

Annex 2.
The tuberculin skin test (TST)

A2.1. Principle of the TST

The TST consists in an intradermal injection of tuberculin (= purified protein derivative, PPD). Tuberculin contains a complex mixture of antigens from mycobacteria including *M. bovis*, *M. tuberculosis* and NTM. Several manufacturers currently produce PPD, and the quantity to be administered will depend on the product (5 standard tuberculin units for PPD-S, 2 tuberculin units of RT23). A quantitative scale named RP30 (Relative potency 30, the protein concentration at which the preparation has 30 % of maximal activity) is used to compare the biological potency of PPD batches and sources, thus standardizing them for clinical use. Although commercialized PPD are hence considered bioequivalent (55) (96), comparative studies show variations between the formulations regarding the relative abundance of several proteins that could influence test results (97). Ideally, to standardize practices and TST interpretation, the same PPD source should be used across the country. PPD RT23 is the tuberculin of choice in Belgium.

Individuals with a cell-mediated immunity against tuberculin antigens will present a delayed-type hypersensitivity reaction at the site of the intradermal injection within 48 to 72 h, although the test can be read up to 5 days after administration. A positive response will result in a localized induration of the skin at the site of injection. The average of two perpendicular transverse diameters of the induration (in mm) is measured by a trained professional. Only the induration should be considered; erythema should not be counted or measured.

A2.2. Execution of the TST

Normally, only one tuberculin is available on the Belgian market: RT23 from AJ Vaccines (ex-Statens Serum Institute) in vials of 1.5 ml of 2 U PPD. In case of stock-out of RT23, it is substituted by Mammalian from Bulbio in vials of 1 ml of 5 U PPD. Both tuberculins are considered to be bio-equivalent. They need to be kept in the refrigerator and the cold chain must be respected during transportation. Once a vial has been opened, its contents should be used within the time period specified by the manufacturer. All manipulation requires that the general rules of asepsis be respected, notably the disinfection of the cap.

The skin must be clean at the injection site. In case alcohol is used to disinfect the skin, it must be completely evaporated before giving the injection.

The administration technique of the two tuberculins is identical: 0.1 ml of the product is injected intradermally using a 1 ml syringe with 100 graduations mounted with a short-bevelled 16 mm needle (gauge number 25 to 27). The tuberculin is injected in the dermis of the external part of the forearm, inserting the needle (with the bevel oriented upwards) parallel to the skin. The fleeting appearance of a pale papule with a diameter of 7 to 8 mm and a “peau d’orange” aspect is evidence that the injection has been given intradermally.

A reaction appearing at the injection site within 48 hours is non-specific and should not be taken into account. The size of the induration (in mm) measured 2-3 to 5 days after the injection with the help of a transparent ruler allows to determine whether the test is positive, negative or doubtful. When interpreting the test, other factors that might influence the reaction need to be

taken into account as well. The same criteria (see tables 4a and 4b in 3.4.1) should be used when interpreting the two tuberculins used in Belgium. When the reaction is very intense, it tends to be accompanied by vesiculation, necrosis, and, occasionally, lymphangitis and satellite adenopathies. These observations should be duly recorded since they are highly specific of reaction due to *M. tuberculosis* infection (98).

A2.3. Allergic reactions and other secondary effects following TST

A localized hypersensitivity immediately following the TST can occur in the form of an erythematous papule at the injection site within 20 min of administration of the TST in 2 to 3 % of patients without a systemic reaction. Local reactions that appear within the first 24 h after injection without the apparition of an induration beyond 48 h are considered non-specific allergic reactions, and usually, don't require any specific treatment. A blistering reaction may occur; it must be kept clean and may be covered with a light bandage, but no ointment should be applied.

A systemic allergic reaction may also occur, ranging from a maculopapular rash to anaphylaxis. The incidence of a systemic allergic reaction is only 1 to 3 per one million doses, similar to those observed for vaccines, and the reported incidence of a severe reaction (anaphylaxis, generalized urticaria, angioedema) is 0,08 - 1 per one million doses (91) (99). Given this low incidence, it is not considered necessary to have a physician present. If the public health authorities have formulated specific precautions related to anaphylactic shock, these are to be observed when administering a TST.

A person that has had an immediate local reaction (including but not limited to blistering) or a systemic reaction can never be tested again with the TST.

Another possible side effect following TST administration is a vaso-vagal reaction. This response occurs in about 7 % of injection-related procedures such as vaccination with BCG; no specific data are available for TST (100). A vaso-vagal reaction is not a contra-indication for future administration of TST.

Annex 3. The IGRA tests

A3.1. Principle of IGRA tests

IGRAs are *in vitro* blood tests that allow for the evaluation of the T-cell mediated response following stimulation by specific MTB antigens. The genes encoding these antigens, namely the early secreted antigenic target 6 (ESAT-6) and culture filtrate protein 10 (CFP-10), are in the region of difference 1 (RD1) of the MTB genome. This region is absent from the genomes of the BCG and of most NTM (except for *M. marinum*, *M. kansasii*, *M. szulgai*, and *M. flavescens*), increasing the specificity of the test for the detection of MTB infection.

IGRA tests need to be performed in a laboratory setting and requires laboratory equipment and trained personnel. Furthermore, since these tests are executed on fresh blood samples, the pre-analytical phase and delay in transportation can reduce the performance of the test. The IGRA test includes negative and positive controls that need to be run in parallel for every sample for a proper interpretation of the test.

Currently, the two commercialized IGRAs for LTBI screening are the QFT®-Plus and the T-SPOT®.TB.

A3.2. QFT®-Plus

Detailed information about the test can be found in the QuantiFERON®-TB Gold Plus (QFT®-Plus) ELISA Package Insert:
http://www.quantiferon.com/wp-content/uploads/2017/04/English_QFTPlus_ELISA_R04_022016.pdf

A3.2.a. How the QFT®-Plus test works

Individuals infected with MTB-complex organisms usually have lymphocytes in their blood that recognize these and other mycobacterial antigens. This recognition process involves the generation and secretion of the cytokine IFN-γ. The detection and subsequent quantification of IFN-γ forms the basis of the QuantiFERON® assay (QIAGEN). QFT®-Plus is the fourth generation of this test.

The clinical assessment of this fourth generation assay is limited. To date, all large-scale studies evaluating the QuantiFERON® technology for LTBI screening have been based on the third generation QuantiFERON® TB Gold In-Tube (QFT®-GIT) that has non-negligible differences with its successor: whereas QFT®-GIT used a single TB tube containing antigens ESAT-6, CFP-10, and TB7.7, QFT®-Plus uses 2 tubes (TB1 and TB2). The TB1 tube contains peptides from ESAT-6 and CFP-10 that are designed to elicit CMI responses from $CD4^+$ T-helper lymphocytes, and the TB2 tube contains an additional set of ESAT-6 and CFP-10 peptides targeted to the induction of CMI responses from $CD8^+$ cytotoxic T-lymphocytes.

In addition to the TB1 and TB2 tubes, the test requires 2 additional tubes: the Nil tube and the Mitogen tube (see table A1):

- The Nil tube contains no antigens and serves as a negative control. The QuantiFERON® technology detects IFN-γ based on a colour reaction: a yellow colour indicates a positive result (presence of IFN-γ). But often, plasma will have a natural yellowish colouring that has nothing to do with IFN-γ production. The colouring detected in the Nil tube corresponds to a non-specific background noise that has to be subtracted from the measurements in the other tubes to arrive at correct results.

- The Mitogen tube is used as a positive control. It contains a substance that stimulates not only the TB recognizing lymphocytes but all lymphocytes in the blood. Therefore, this tube should always show the presence of IFN-γ.

Table A1. Blood collection tubes QFT®-Plus

Tube	Color	Stimulation
QuantiFERON Nil Tube	Grey	Negative control
QuantiFERON TB1 Tube	Green	$CD4^+$ cells
QuantiFERON TB2 Tube	Yellow	$CD4^+$ cells + $CD8^+$ cells
QuantiFERON Mitogen Tube	Violet	Positive control

A3.2.b. Execution of the test

Whole blood is collected into the four tubes (1 ml per tube). Once blood is collected up to the black mark on the side of the tubes, each tube must be turned gently ten times, just firmly enough to make sure that the entire inner surface of the tube is coated with blood. A complete coating will dissolve antigens on tube walls. Tubes must then be transferred at room temperature to the laboratory for incubation (as soon as possible, and within 16 hours of collection).

In the laboratory, the tubes are incubated at 37°C. Following a 16 to 24 hours' incubation period, the tubes are centrifuged, the plasma is harvested and an ELISA assay is performed to measure the IFN-γ levels (IU/ml) in each tube.

A3.2.c. Interpretation of the test results in the laboratory

The software provided by the manufacturer automatically interprets the QFT®-Plus results according to table A2.

Table A2. Interpretation of QFT®-Plus results based on the software provided by the manufacturer

Nil (IU/ml)	TB1 minus Nil (IU/ml)	TB2 minus Nil (IU/ml)	Mitogen minus Nil (IU/ml)	QFT-Plus Result	Report/Interpretation
≤ 8.0	≥ 0.35 and ≥ 25 % of Nil	Any	Any	Positive	*M. tuberculosis* infection likely
	Any	≥ 0.35 and ≥ 25 % of Nil			
	< 0.35 **OR** ≥ 0.35 and < 25 % of Nil		≥ 0.5	Negative	*M. tuberculosis* infection NOT likely
			< 0.5	Indeterminate	Likelihood of *M. tuberculosis* infection cannot be determined
> 8.0	Any				

The Nil tube adjusts for background noise such as excessive levels of circulating IFN-γ or presence of heterophile antibodies. This can also happen in case of poor blood sampling: lysis of the red blood cells will result in a colour reaction that is too intense and disturbs the detection of IFN-γ. If the Nil tube shows a very high natural colouring (> 8.0) this will disturb the proper interpretation of the test. The result is shown as indeterminate and the test should be repeated.

The Mitogen tube does not have to be taken into consideration if any of the test tubes (TB1 or TB2) is positive. If the test tubes are negative, the Mitogen tube should be positive (≥ 0.5). If this is not the case, it may be the result of insufficient lymphocytes, reduced lymphocyte activity due to incorrect filling/mixing of the Mitogen tube, improper specimen handling or incubation, or inability of the patient's lymphocytes to generate IFN-γ. The test cannot be interpreted and needs to be repeated to exclude a technical problem. If there is doubt as to the individual's immune status (e.g. advanced HIV infection), a lymphocyte count needs to be performed.

When sending the test result to the requesting clinician, the laboratory should not simply give the results as positive or negative but also include the quantitative results of the test. Several studies have demonstrated the existence of a borderline zone equivalent to the doubtful result of the TST. Although official cut-offs have not been established, the borderline zone of the QFT®-Plus is likely to be between 0.2 and 0.7 IU/ml (101).

It is suggested that the result sent out by the laboratory should contain the following information:

Test result	TB1 measurement	TB2 measurement
☐ Positive	Value in IU/ml	Value in IU/ml
☐ Negative		
☐ Indeterminate	Take new sample and repeat the test	

A key to interpreting the TB1 and TB2 values may be added:

	Value observed in either TB1 or TB2				
	< 0.2	0.2 – 0.35	0.35	0.35-0.7	> 0.7
Interpretation	Negative	Borderline negative	Cut-off	Borderline positive	positive

It is recommended to repeat the test in case of a borderline positive or borderline negative result.

Results from QFT®-Plus testing must be used in conjunction with each individual's epidemiological history, current medical status and other diagnostic evaluations.

A3.3. T-SPOT®.TB

Detailed information about the test can be found in the T-SPOT®.TB Package Insert:
http://www.tspot.com/wp-content/uploads/2012/01/PI-TB-US-v5.pdf

The T-SPOT®.TB (Oxford Immunotec) is a test based on the enzyme-linked immunospot (ELISPOT) technology. It does not measure the plasmatic levels of IFN-γ but rather the abundance of effector T-cells, both $CD4^+$ and $CD8^+$, producing IFN-γ following stimulation with MTB antigens (a combination of peptides simulating ESAT-6 and CFP-10 antigens). The test requires the separation, washing and counting of peripheral blood mononuclear cells (PBMC) from whole blood samples before stimulation.

Whole blood must be collected in Heparin-Lithium tubes (5-10 ml, preferably 10 ml if lymphopenia). Tubes must be shaken ten times before being sent to the laboratory at room temperature within 8 hours of sampling, except when the T-Cell Xtend reagent is used, extending the period to 32 hours. The reagent must be added to the whole blood prior to sample processing.

In the laboratory, PBMCs will be isolated using density-gradient centrifugation and distributed equally into wells pre-coated with IFN-γ specific antibodies. For each sample, 4 wells are used:
- Nil Control (containing no antigens);
- Panel A (containing ESAT-6 antigens);
- Panel B (containing CFP-10 antigens);
- Positive Control (containing a Mitogen).

After 16 to 20 hours' incubation at 37°C, ELISPOT technology is used and the number of "spots" (IFN-γ producing cells) are counted. The spots produced as a result of antigen-stimulation appear as distinct, large, round and dark blue spots. Typically, there should be few or no spots in the Nil Control. A spot count in excess of 10 spots should be considered as 'Invalid'. The Positive Control spot count should be ≥ 20 or show saturation (too many spots to count). If the Positive Control spot count is < 20 spots and both Panel A minus Nil and Panel B minus Nil have ≤ 4 spots, the result should be considered as 'Invalid'. In the case of Invalid results, it is recommended to collect a further sample and re-test the individual.

Results for the T-SPOT®.TB test are interpreted by subtracting the spot count in the Nil Control well from the spot count in each of the Panels, according to the following algorithm (see figure A1):

- The test result is Positive if (Panel A minus Nil) and/or (Panel B minus Nil) ≥ 8 spots.
- The test result is Negative if both (Panel A minus Nil) and (Panel B minus Nil) ≤ 4 spots. This includes values less than zero.
- Results where the highest of the Panel A or Panel B spot count is such that the (Panel minus Nil) spot count is 5, 6 or 7 spots should be considered Borderline (or equivocal) and retesting by collecting another patient specimen is recommended.
- If the result is still Borderline on retesting with another specimen, then other diagnostic tests and/or epidemiologic information should be used to help determine TB infection status of the patient.

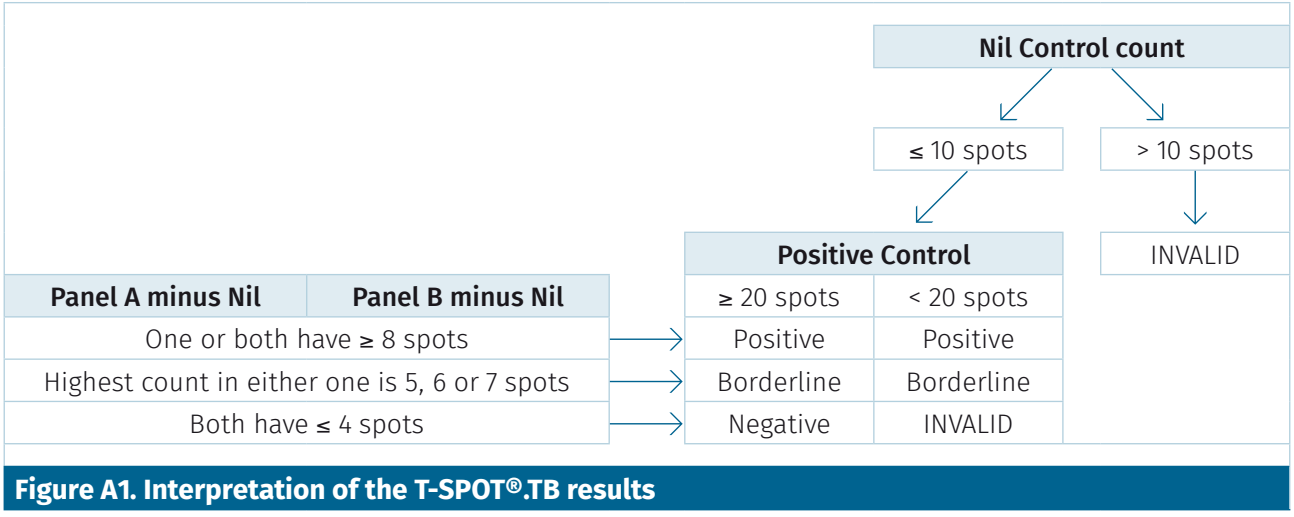


Figure A1. Interpretation of the T-SPOT®.TB results

A3.4. Allergic reactions and secondary effects of IGRA tests

As the test is done *in vitro*, allergic reactions and secondary effects are not possible, with the exception of complications of the standard venipuncture.

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