BELGIAN GUIDELINES
ON THE DIAGNOSIS AND MANAGEMENT OF TUBERCULOSIS INFECTION

2025 (2nd Edition)

These guidelines were developed in 2019 by the following members of the LTBI Working Group of the Scientific Committee Tuberculosis of the Belgian Lung and Tuberculosis Association (BELTA):

Prof Steven Callens, chair, infectiologist, UGent/UZGent
Dr (PhD) Laetitia Aerts , microbiologist, ULB
Prof Emmanuel André, microbiologist, KULeuven/UZ Leuven
Dr Wouter Arrazola de Oñate, medical director, VRGT/BELTA
Prof Emmanuel Bottieau, infectiologist, Institute Tropical Medecine, Antwerp
Prof Iris De Schutter, pediatrician, UZ Brussel
Dr Annie Drowart, pulmonologist, CHU Brugmann
Dr Guido Groenen, coordinator, BELTA-TBnet
Dr (PhD) Vanessa Mathys, microbiologist, Belgian National Reference Centre for mycobacteria, Sciensano
Dr Filip Moerman, infectiologist, CHR Citadelle Liège
Dr Françoise Mouchet, pediatrician, CHU Saint-Pierre/ULB
Dr Jean-Pierre Rézette, occupational medicine, CHU Charleroi
Dr Kinda Schepers, infectiologist, ULB
Prof Eva Van Braeckel, infectiologist, UGent/UZGent
Prof Jean-Paul Van Vooren, infectiologist, ULB
Dr Maryse Wanlin, director, FARES/BELTA
Dr Chloé Wyndham-Thomas, internist, Sciensano

The main change included in the 2025 2nd edition concerns the chapter 4 “Treatment of (latent) TB infection”, since rifampicin is now reimbursed for preventive treatment under the same conditions as for the treatment of active TB disease, in Belgium. This allows more regimen’s options for the preventive TB treatment.

Thanks to Prof Steven Callens for his scientific review, Dr Inge Muyle for her practical judgement and Drs Koen Vanden Driessche and Oriane Stevart for their help in regards of paediatric issues.

Dr Vinciane Sizaire, director, FARES/BELTA

Colofon
BELTA/FARES/VRGT, June 2019, Brussels, Belgium
Eendrachtstraat/Rue de la Concorde 56, 1050 Brussels
LTBI@fares.be (French) / LTBI@vrgt.be (Flemish)

Suggested citation
BELTA/FARES/VRGT, Belgian Guidelines on the Diagnosis and Management of Latent Tuberculosis Infection, June 2019

Layout: Nathalie da Costa Maya, www.cdcsasbl.be
Cover: shutterstock / blau ananas

TABLE OF CONTENT

ABBREVIATIONS **5**

1. INTRODUCTION **7**

2. THE NEED TO ADDRESS TBI **8**

3. TBI TESTING **11**

3.1. Who needs to be tested for tuberculosis infection **11**
3.1.1. Risk factors for TBI evolving into tuberculosis 11
3.1.2. Groups to be tested for TBI 12
3.1.3. Testing in children 13
3.1.4. Testing in specific situations 13
3.1.4.a. Pregnancy and post-partum 13
3.1.4.b. Ageing persons 13
3.1.4.c. Persons living with HIV 14
3.1.4.d. People with fibrotic lesions on chest X-ray 16
3.1.4.e. Travellers and/or expatriates 17
3.1.4.f. Professionals with high risk of exposure to tuberculosis 17
3.1.4.g. Other risk groups for whom TBI testing can be considered 18
3.2. Which tests are available to screen for tuberculosis infection **19**
3.3 How to decide which test to use **20**
3.3.1. General approach 20
3.3.2. TBI testing in children 22
3.3.3. TBI testing during pregnancy 24
3.3.4. TBI testing in PLHIV 24
3.3.5. Summary: TST or IGRA? Or both? 25
3.3.5.a. Situations in which TST is preferred 25
3.3.5.b. Situations in which IGRA is preferred 25
3.3.5.c. Situations in which TST and IGRA can be used consecutively to increase sensitivity 26
3.3.5.d. Situations in which TST and IGRA can be used consecutively to increase specificity 26
3.4. How to interpret the TST and IGRA test results **26**
3.4.1. Interpretation of TST 26
3.4.1.a. Risk stratification 26
3.4.1.b. Negative screening results in contacts 28
3.4.1.c. Doubtful TST result 28
3.4.1.d. False positive TST results 29
3.4.1.e. False negative TST results 30
3.4.1.f. Conversion of TST 31
3.4.1.g. Reversion of TST 31
3.4.1.h. Booster effect of TST 31
3.4.2. Interpretation of IGRA 32
3.4.2.a. Interpretation of the QFT®-Plus test 32
3.4.2.b. Interpretation of T-SPOT®.TB test 33

3.4.2.c. Negative screening results in contacts 33
3.4.2.d. Indeterminate, invalid and borderline IGRA result 34
3.4.2.e. False positive IGRA results 34
3.4.2.f. False negative IGRA results 34
3.4.2.g. Booster effect of IGRA 35
3.4.2.h. Conversions and reversions of IGRA 35
3.4.2.i. Reproducibility of IGRA tests 35

4. TREATMENT OF TUBERCULOSIS INFECTION 36

4.1. Who should be treated for TBI 36
4.1.1. General consideration 36
4.1.2. Approach in specific situations 37
4.1.2.a. Children 37
4.1.2.b. Poeple living with HIV 38
4.1.2.c. Pregnancy, postpartum and lactation 38
4.1.2.d. Presence of fibrotic lesions on chest X-ray 38
4.1.3. Preventive treatment for contacts of multidrug-resistant tuberculosis cases 38
4.2. Treatment regimens for TB preventive treatment 39
4.2.1. General considerations 39
4.2.2. TPT regimens recommended in Belgium 39
4.2.3. For specific patients 41
4.2.3.a. Woman and pregnancy 41
4.2.3.b. HIV patients 41
4.2.3.c. When INH treatment is prescribed 41
4.3. Before starting TPT 42
4.4. Follow-up during treatment 43
4.4.1. Routine monitoring 43
4.4.2. Ensuring adherence to treatment 43
4.5. Managing side effects 45
4.5.1. Isoniazid 45
4.5.1.a. Hepatotoxicity 45
4.5.1.b. Peripheral neuropathy 45
4.5.2. Rifampicin 45
4.5.3. Levofloxacine 46
4.5.4. Drug Interactions 46
4.6. After the TBI treatment has been completed 47

ANNEXES 48

Annex 1. The tuberculin skin test (TST) 48
A1.1. Principle of the TST 48
A1.2. Execution of the TST 48
A1.3. Allergic reactions and other secondary effects following TST 49
Annex 2. The IGRA tests 50
A2.1. Principle of IGRA tests 50
A2.2. QFT®-Plus 50
A2.2.1. How the QFT®-Plus test works 50
A2.2.2. Execution of the test 51
A2.2.3. Interpretation of the test results in the laboratory 51
A2.3. T-SPOT®TB 52
A2.4. Allergic reactions and secondary effects of the IGRA tests 53

REFERENCES 54

ABBREVIATIONS

AIDS	Acquired immunodeficiency virus
BCG	Bacillus Calmette-Guérin
BELTA	Belgian Lung and Tuberculosis Association
cART	Combination antiretroviral therapy
CD4+	Cluster of differentiation 4
CDC	Centers of Disease Control
CFP-10	10 kDa culture filtrate antigen (antigen produced by *M. tuberculosis*)
CMI	Cell mediated immunity
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
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
TBI	Tuberculosis infection
TNFα	Tumor necrosis factor alfa
TPT	Tuberculosis Preventive Treatment
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 (TBI) is to provide guidance on:

- how to identify and prioritize at-risk population groups who would benefit from TB Infection testing and treatment;
- how to provide preventive TB treatment (TPT) to those who need it.

The 2019 1st edition guidelines were an update of an earlier document, published in 2003 (1), reviewed at the light of WHO (2), ERS (3) and NICE (4) guidelines on the management of LTBI, published in 2015.

This 2nd edition keeps the recommendations on the identification of individuals for TBI testing and treatment, the algorithmic approach to test and treat TBI and presents an update about the preventive treatment options in Belgium. Indeed, since May 2024, rifampicin is reimbursed for preventive treatment under the same conditions as for active TB disease treatment. Therefore, physicians have the possibility to prescribe the shorter RMP containing regimens without constrains. The 2024 WHO consolidated guidelines on tuberculosis preventive treatment (5) support the new recommendations on preventive treatment of this new edition.

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.

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

WHO has also updated its terminology from “Latent Tuberculosis Infection (LTBI)” to “Tuberculosis Infection (TBI)” to more accurately reflect the spectrum of TB infection. This change acknowledges that TB infection exists on a continuum, ranging from asymptomatic infection to disease, without a clear demarcation between latent and active states. The term “TBI” encompasses all forms of TB infection, irrespective of clinical manifestations and the current WHO definition of Tuberculosis Infection (TBI) is: “a state of persistent immune response to stimulation by Mycobacterium tuberculosis antigens with no evidence of clinically manifest TB disease” (5).” The new terminology will also be used in this 2nd edition.

Thus, LTBI becomes TBI for TB Infection and LTBI treatment becomes TPT for TB Preventive Treatment.

2. THE NEED TO ADDRESS TBI [1]

Belgium is classified as a low-incidence country according to the definition of the WHO (6) 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 (7). 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 cases with tuberculosis will not be sufficient to reach these goals. Individuals that are infected but not symptomatic represent a large reservoir of potential future tuberculosis that must also be addressed. Indeed, the preventive treatment of TBI 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 infected with *Mycobacterium tuberculosis* (8). 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 TBI is detected. Once tuberculosis disease has been excluded, TB preventive treatment (TPT) 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 tuberculosis burden. Importantly, most such cases of tuberculosis do not generally result in major disease outbreaks, probably as a result of well-functioning public health systems (that include TBI screening and treatment) (9).

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" (no symptoms)

1 TBI is the new WHO terminology for LTBI.

occurs when the host immune responses control bacterial replication 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.

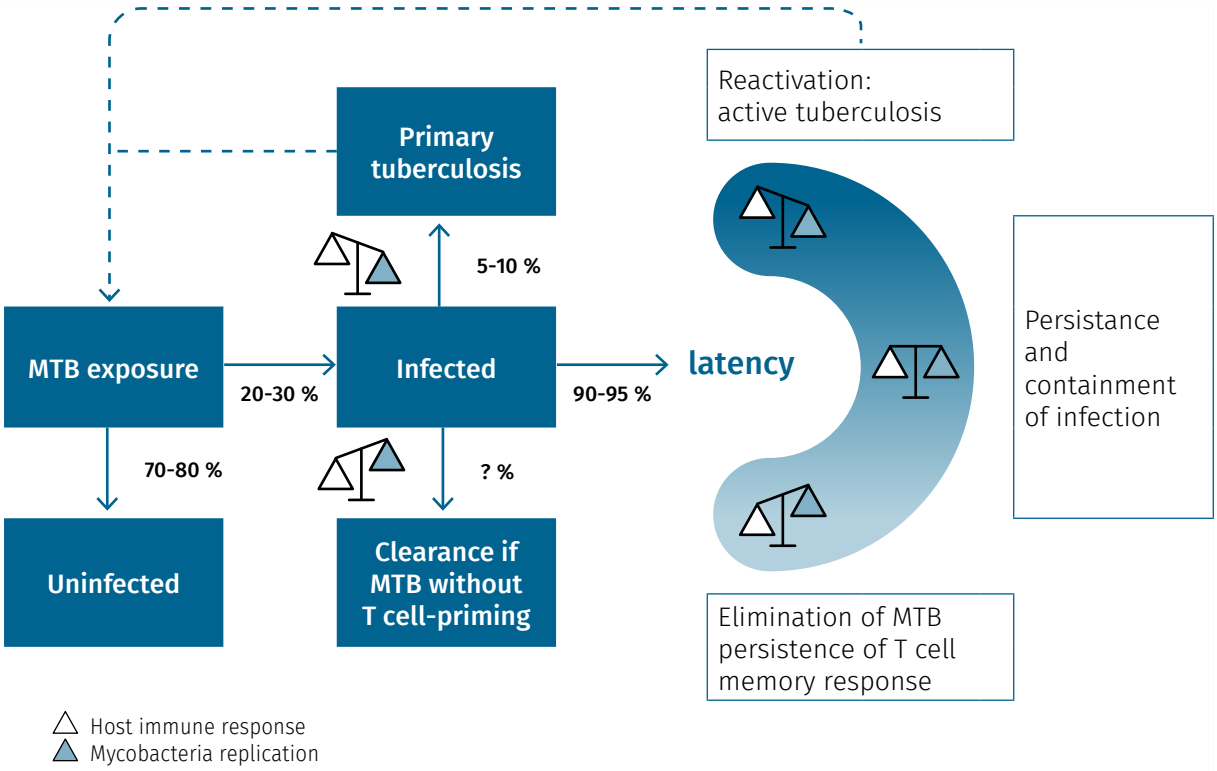


Figure 1. Pathogenesis of TB infection, adapted from reference (10)

The lifetime risk of developing a tuberculosis for a person with documented TBI is estimated to be 5–15 %, with the majority developing TB within the first five years after primary infection (10). 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 % (11). If no disease develops within five years, the remaining lifetime risk might be as low as 2 %, and 0.5 % after ten years (12). The most recent analysis of multiple longitudinal epidemiological studies, however, shows that the majority of tuberculosis manifests itself soon after infection, with disease rarely occurring more than two years after infection (9). Although bacterial, host and environmental factors will together determine the likelihood of progressing from infection to clinical TB, it is the immunological status of the host that is of particular importance (13).

Immunodeficiency, and in particular advanced HIV infection with severe immunodepression, is a major risk factor for the development of tuberculosis. 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 tuberculosis with a steep 44 % to 80 % drop in TB incidence, depending on the setting (14) (15).

In non-endemic countries, the risk of tuberculosis in HIV-infected patients under cART remains higher than in the general population but with low incidence rates (1.64/1,000 person-years) (16).

The reactivation of TB can be averted by preventive treatment. Currently available regimens for the treatment of TBI 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 (17). 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 tuberculosis, 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 TBI (18). Improvements in the management of TBI 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 TPT, older age (i.e. > 35 years) and the perception of risk and severity of TBI (18).

These findings suggest a need to properly define the goal of TBI 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 tuberculosis. The immunodeficiency disorders requiring TBI 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 TB preventive treatment (4.1.2.b) is proposed for PLHIV. TBI 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 TBI related issues in immunocompromised hosts, it may be wise to seek expert advice.

3. TBI TESTING

3.1. WHO NEEDS TO BE TESTED FOR TUBERCULOSIS INFECTION

3.1.1. Risk factors for TBI evolving into tuberculosis

Although most individuals with TBI control the infection and are asymptomatic, the risk of progression to tuberculosis remains. It is, therefore, crucial to identify those at the highest risk of progression to tuberculosis, 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 tuberculosis. Table 1 shows the principal risk factors to consider, while Table 2 shows the age related risk.

Table 1. Risk of developing tuberculosis in individuals infected with MTB
Adapted from (19) (20)

Risk factor	Relative risk of developing tuberculosis compared to an individual without risk factors
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 tuberculosis in immunocompetent children following TBI (21)

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 TBI

The group listings below are based on the WHO and ECDC recommendations (5) (22).

Systematic testing and TPT 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 (23)
- Patients initiating immunosuppressive therapy[2], 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 TPT should be considered for:
- Prisoners
- High-risk immigrants from high-burden countries[3], i.e. asylum seekers aged less than 5 years and pregnant women
- 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 TBI 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.

2 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 updated incidences to be found on https://data.who.int/indicators/i/13B4226/C288D13 (high incidence if > 100/100,000)

3.1.3. Testing in children [4]

During contact tracing, children deserve specific attention because they are at high risk of developing tuberculosis, 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 [5]. If a child aged less than 5 years tests negative on first TBI 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 tuberculosis, 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 (24).

In children, prior BCG vaccination is never a contraindication for TBI testing (25). A single BCG vaccine at birth usually leads to a positive TST that wanes over the next decade (19) (26). In children who received vaccination during the newborn period (days 1 to 28), 85 % lost reactivity within two to three years (27). By the age of 10 years less than 1 % of children had a TST of 10 mm or greater (28).

3.1.4. Testing in other specific situations

3.1.4.a. Pregnancy and postpartum

Pregnancy does not constitute a risk factor for tuberculosis 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 (29).

For women at risk of TB, pregnancy provides an important opportunity to screen for TBI. As women are already in care, acceptance of TBI testing and chest radiography is high. During post-partum, 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 (30).

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.

4 Child: aged 0 - 15 years of age

5 Data from the national tuberculosis registers 2010-2017:
https://tuberculose.vrgt.be/informatiebank?term=&cid %5B23 %5D=23 (Flemish)
https://fares.be/documentation/tuberculose (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.

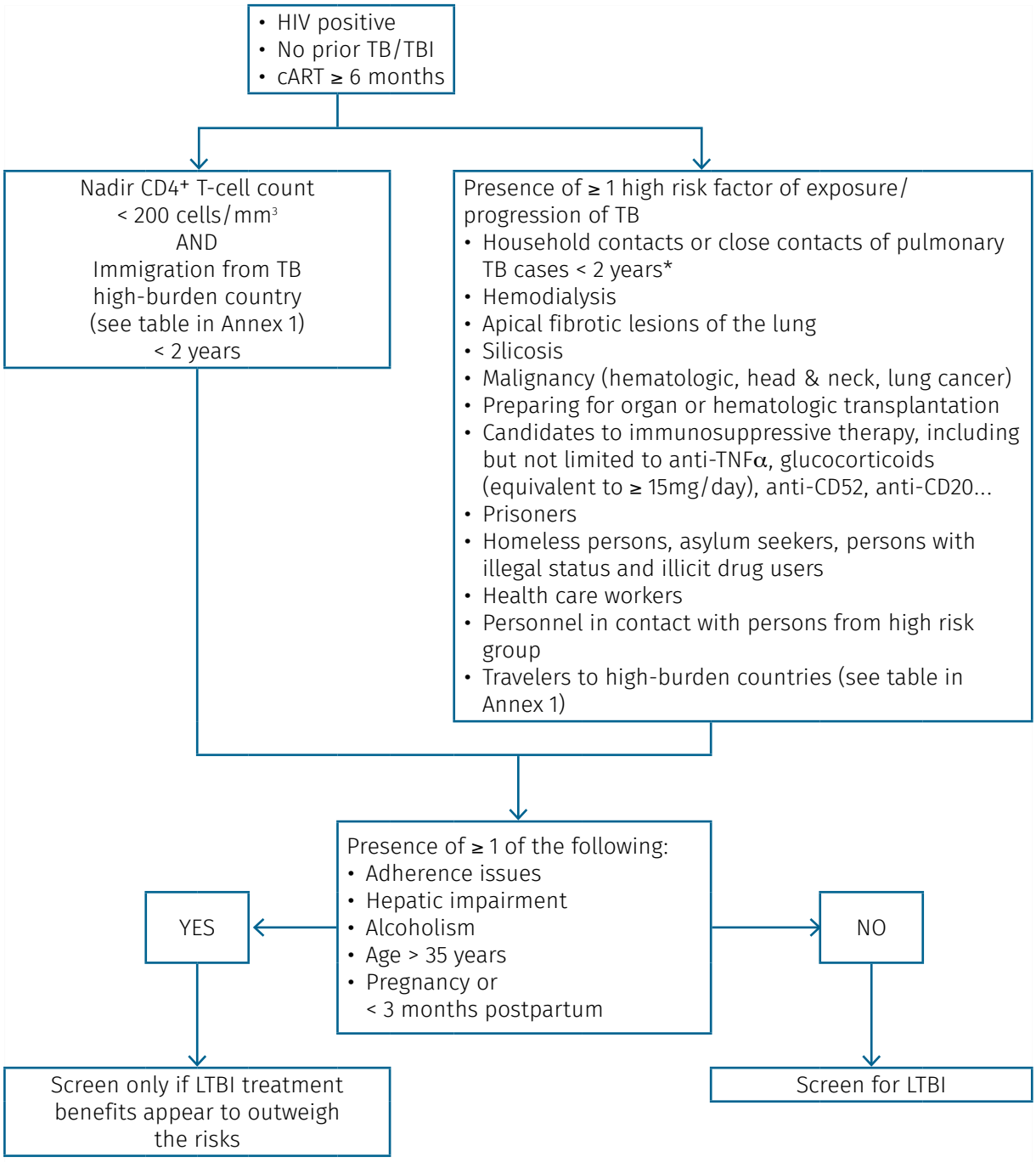
Universal screening for TBI at entry in a facility is not recommended:
- TBI testing must lead to a decision to treat preventively in the event of a positive outcome. However, the "intention to screen is intention to treat" principle is rarely applied in view of the increased hepatotoxicity of isoniazid (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 (30).

3.1.4.c. Persons living with HIV (PLHIV)

Treatment for TBI has shown to decrease risk of tuberculosis in HIV-infected persons, with an additional benefit to cART (31) (32) (33). However, defining a TBI 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 TPT to cART in non-TB endemic settings, as all studies have taken place in sub-Saharan Africa (31) (33). Secondly, the sensitivity of TST and IGRA is reduced in the context of HIV-infection, with a sharp fall with declining $CD4^+$ count (34). This is particularly problematic as it is the people with the lowest $CD4^+$ count that are at the highest risk of developing tuberculosis. 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, and in accordance with the Belgian AIDS reference centres, the following key points are suggested for TBI screening in PLHIV (23):
- Target population:
  - Screening for TBI should be considered for HIV-infected persons with a baseline $CD4^+$ T-cell count below 200 cell/mm3 AND with history of immigration from a high-burden TB country (see table in Annex 1) in the past 2 years.
  - Screening for TBI should be considered for HIV-infected persons with ≥1 high risk factor of exposure to *M. tuberculosis* or progression to tuberculosis (see figure 2).
- Timing of screening:
  - Screening for TBI 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 TBI, after exclusion of tuberculosis, regardless of TBI 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 TBI regardless of TBI test result (see 4.1.2.b)

Figure 2. When to screen for TBI in PLHIV (based on reference 23)

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

Little information is available in the recent literature on the statistics of TBI in fibrotic lesions, and references cite the major studies performed in the 1970s (35) (36) (37).

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 (35) (38).

Fibrotic lesions are important for three reasons (35):
1. There is a risk of tuberculosis in the future.
2. Misdiagnosis of fibrotic lesions can mask smear-negative tuberculosis, and there is a danger of starting TPT single-agent therapy that may lead to acquired resistance or failure to treat. Conversely, misdiagnosis of fibrotic lesions as tuberculosis 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 (35):
- The maturity of the lesions: the risk of reactivation TB 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 tuberculosis.
- 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 (39).
- If TST conversion is recent, there is a higher chance of tuberculosis.
- The more extensive the scarring, the greater the bacillary load of the initial TB. If lesions with cavitation, non-calcified adenopathies, and/or pleural effusion are present, even if smear or culture negative, tuberculosis should be excluded.

The differential diagnosis of fibrotic lesions includes all pulmonary processes that may present with radiological features that look like pulmonary tuberculosis. Careful clinical evaluation and appropriate complementary examinations must be used to rule out an alternative diagnosis, taking into consideration risk factors for tuberculosis (35).

In the absence of clinical symptoms suggesting tuberculosis, a follow-up X-ray should be performed after three months (and even one month if lesions are extensive), while waiting for the culture results (35). If TBI testing is negative, an alternative diagnosis should be sought, and appropriate clinical follow-up done.

3.1.4.e. Travelers and/or expatriates

Travellers can be subject to screening for TBI under specific circumstances. Indeed, a conversion of TST test has been observed at a rate of 3 to 4 % in long-term travellers and expats from the Netherlands and United States and can reach as high as 12 % in person employed or volunteering in health care settings (40). Nevertheless, screening for TBI should only be carried out among travellers at greatest risk of acquiring TB (e.g., volunteers, long-term adventurous travellers, backpackers...) (41). Another group deserving particular attention are children born in Belgium who travel to an endemic country for family visits.

Travellers fulfilling the following criteria can be identified as candidates for TBI 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 TPT if a conversion has occurred following exposure. Documenting TST before travel is important in travellers identified as candidates for TBI screening after their return. Screening with a TST in a very low-risk population of travellers 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 (42).

If TBI is diagnosed, the indication to start TPT should be assessed on a case-by-case basis with an expert, as the risk of progression to tuberculosis might be extremely low when diagnosed before the actual travel. After travel, screening for TBI should be repeated at six weeks to 3 to 4 months after return, if TBI test proved negative before travel (40).

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 (30). 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 TBI testing 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 TPT 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 patients with tuberculosis 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 TBI and should be retested semi-annually.

B. Employees who are occasionally exposed to patients with tuberculosis 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 TBI 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 TBI testing can be considered

In 3.1.2 it has been mentioned that testing and treatment of TBI 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 TBI testing are explained in the respective recommendations [6].

3.2. WHICH TESTS ARE AVAILABLE TO SCREEN FOR TUBERCULOSIS INFECTION

Direct detection of MTB can only be achieved at the site of bacterial replication of persons suffering from tuberculosis. Therefore, the presence of TBI can only be detected indirectly. Currently, there are two immunodiagnostic tests available for TBI screening, 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 (43). 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 TBI, and all tests have been evaluated in patients with tuberculosis. Also, these tests cannot discriminate TBI from active tuberculosis. For this reason, before treating TBI, tuberculosis should always be ruled out using conventional means. In general, symptom screen for elements suggestive of tuberculosis (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

6 Prison strategy:
https://tuberculose.vrgt.be/sites/default/files/Richtlijnen%20tuberculose%20gevangenissen%20Belgie%CC%88%202007_0_0.pdf (Flemish)
https://fares.be/documentation/tuberculose (French; baseline document)
Asylum seekers strategy:
https://fares.be/documentation/tuberculose (French)
https://tuberculose.vrgt.be/sites/default/files/TBC%20preventie%20bij%20asielzoekers%20-%20strategie%20voor%20Fedasil%20centra.pdf (Flemish)

out tuberculosis (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 tuberculosis, immunodepression and other risk factors...). It is important to note that besides the scientific data, practicality and financial implications are considered important in determining the test strategy in individual cases and institutions.

Table 3. Characteristics of TST and IGRAs. Adapted from (44) (45)

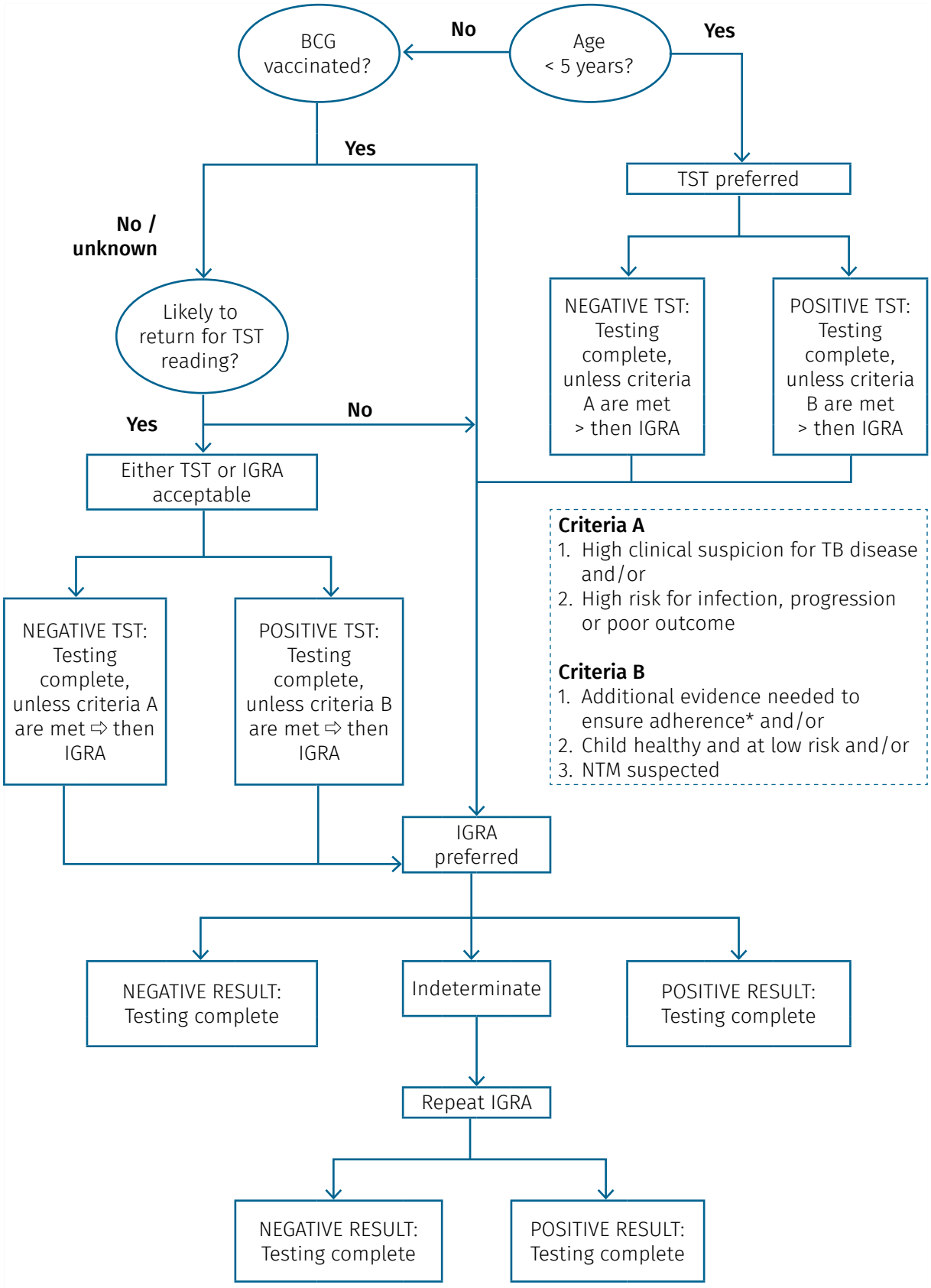
Characteristics	TST	IGRA
Number of visits	2	1
Time to read-out of results	48-120 h	24 h
Trained personnel required	yes	yes
Blood sampling needed	no	yes
Intradermal injection needed	yes	no
Need for laboratory equipment	no	yes
Cross-reactivity with BCG	yes	no
Cross-reactivity with NTM	yes	unlikely
Conversions /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 (46) (47)	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 (46) (47) (48)	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. TBI testing in children

The purpose of TBI 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 TBI 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 a TB case or other risk factors for infection or progression to tuberculosis.

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 (49) 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 (46) (47) (50). 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) (51) (52). 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 48)

3.3.3. TBI 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 (29).

3.3.4. TBI testing in PLHIV

Screening for TBI should be made using a two-step approach (see figure 4):
- Initial screening by TST. An induration of ≥ 5mm in diameter is considered positive.
- If TST is negative, perform IGRA within 72 hours of tuberculin injection to avoid false positivity of the IGRA (53).

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

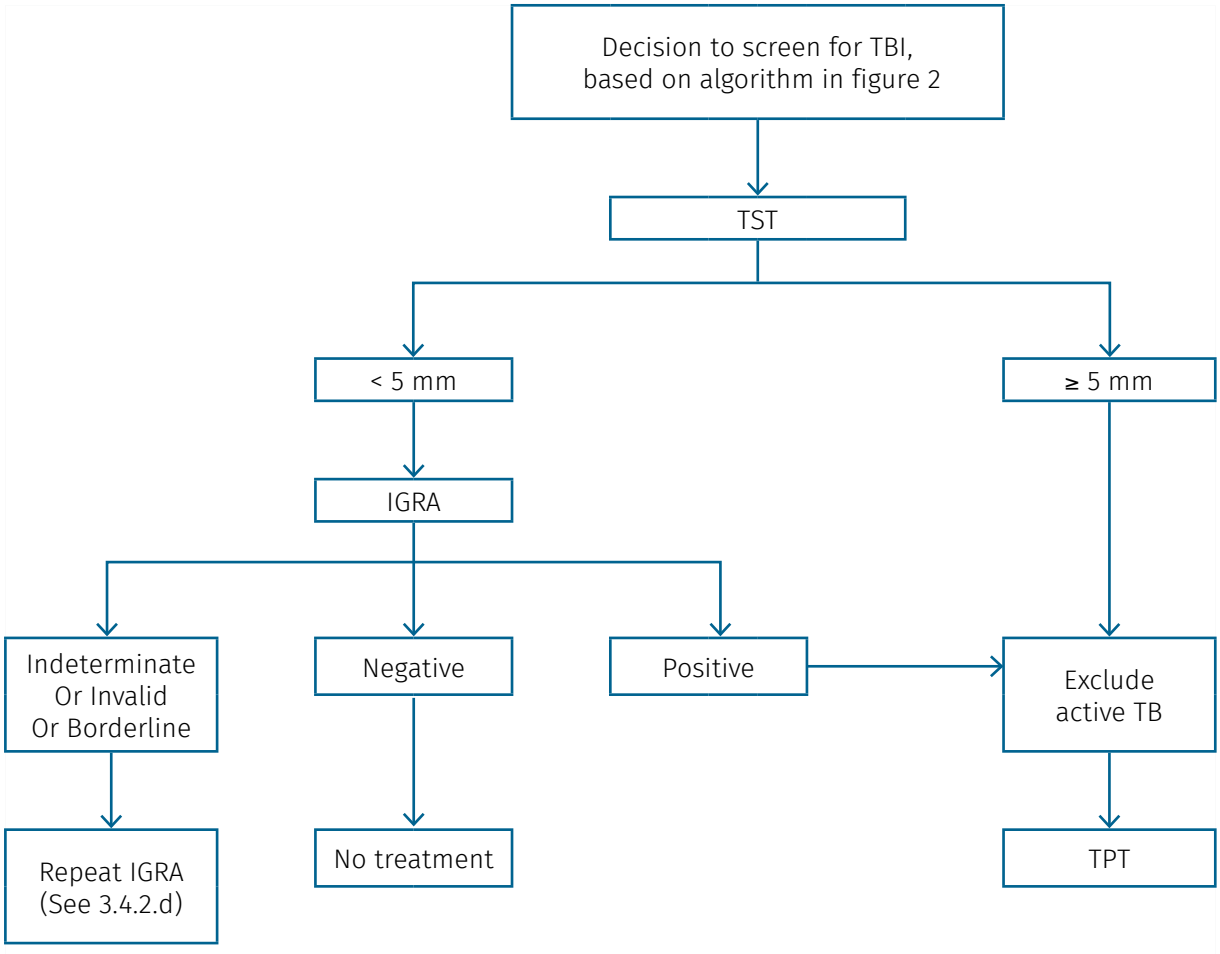


Figure 4. How to screen for LTBI in PLHIV (based on reference 23)

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 (53).

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 contagious 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
- Adult with a 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 (54). 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 tuberculosis 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 TPT and adhere to it.

IGRA should be done within 72 hours to avoid false positivity of the IGRA (54), or both tests can be done simultaneously.

3.4. HOW TO INTERPRET THE 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, 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) (55)
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[6]	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 tuberculosis: 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
≥ 15 mm	Positive	

7 Using different TST size cut-offs for BCG vaccinated and unvaccinated children is not a universal policy. A recent review of national and international childhood TB guidelines found that most countries and agencies use a 10 mm induration cut-off for all children irrespective of BCG vaccination status (30), in line with the advice of WHO. WHO recommends treating all children aged < 5 years for TB infection following significant exposure to an infectious TB case, irrespective of the result of the test of TB infection and irrespective of BCG vaccination status (31), while the 2016 NICE (UK) guideline recommends treating all children for TB infection if they have a TST result ≥ 5 mm independent of IGRA result and BCG vaccination history (4).

3.4.1.b. Negative screening results in contacts

A negative TBI 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, TBI 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 (24) 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 TST testing after 8 weeks is not indicated. TPT 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 (56) (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 tuberculosis 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 of 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 TPT. 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 % (57). 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 (57).

- 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 (58).

  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 (59).

– 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	• Tuberculosis (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 (60).
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 TBI.

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 (30). 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 tuberculosis. 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 6mm, but alternate criteria have been suggested based on the prevalence of boosting in a particular population (61). 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 (62). 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 (63). 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 TPT 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 TPT.

3.4.2. Interpretation of IGRA

Assessing the probability of TBI 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 (64) 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 will be interpreted according to 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 TPT 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 tuberculosis. 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 of 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 tuberculosis.

- Both immunological and technical phenomena (64) 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 (60).

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 (65). This amplification appears after 72 hours and disappears within three months (65). 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 (64).

4. TREATMENT OF TUBERCULOSIS INFECTION

4.1. WHO SHOULD BE TREATED FOR TBI [8]

4.1.1. General considerations

Treatment of TB infection is essential to controlling and eliminating TB because it substantially reduces the risk that TB infection will progress to Tuberculosis. Currently preventive treatment regimens have an efficacy ranging from 60 % to 90 %. The protection of these treatments can last up to 19 years in low endemic countries, such as Belgium (11).

The decision to treat TB infection should be based on a comprehensive evaluation of the individual context and a careful analysis of risks and benefits of the preventive treatment, rather than test results alone.

If either the TST or the IGRA is positive, treatment is strongly recommended. This is particularly true for populations at high risk of exposure and/or developing the disease once infected (see table 1 in chapter 3.1.1). It includes:

- Recent contacts of tuberculosis cases
- Children under the age of 5
- HIV-positive patients
- Immunocompromised patients
- Patients starting TNF-α inhibitors
- Patients with fibrocystic lesions
- TST conversion in the frame of health occupational systematic screening

The use of both a TST and an IGRA in TBI screening is limited to specific situations and often leads to discordant results (66). 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, TPT should be considered if the risk to develop TB is high (e.g., immunodepression, recent contact...).
c. In BCG vaccinated individuals, evaluate the possibility of a false positive TST result based on the considerations in 3.4.1.d.

8 TB Infection is the new WHO terminology for LTBI.

Table 8. Guidance for the interpretation of TBI testing when both results for TST and IGRA are available (67)

	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 TPT			Consider TPT	TPT is not necessary	Consider NTM. Seek advice from specialist	Repeat IGRA test or base interpretation on TST result
TST Doubtful	Consider TPT	Repeat TST	Consider TPT	Consider TPT	TPT is not necessary		Repeat IGRA
TST Negative	Consider TPT	TPT is not needed except in immuno-depressed contacts	Repeat IGRA test or base interpretation on TST result	Consult a TB specialist to consider TPT	TPT is not necessary		

4.1.2. Approach in specific situations

4.1.2.a. Children (2) (7) (68)

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

- A child, aged less than 5 years with a negative test for TB infection but exposed to a case of pulmonary TB, especially if the index case is contagious, should receive "window prophylaxis", after an appropriate clinical evaluation (i.e. history, symptoms, radiological and microbiological exams if needed) has excluded tuberculosis in this child. Be particularly vigilant for TB meningitis, as typical signs may be absent in the early stages (cfr 4.3).

- A second test should be conducted 8 to 12 weeks after the last contact, even if the TPT has been completed, in case of a short regimen, to confirm TB infection. Whatever are the results of this second test, close monitoring by the paediatrician to exclude tuberculosis remains necessary, especially for children under 5 years of age. A positive test result indicates that the TPT should continue until completion. If the second test is negative, it may sometimes be a false negative, particularly in young children. A false negative test is always suspected in children under 6 months old. If a false negative is suspected, the TPT should still be completed and the child should be monitored after the end of the treatment. In immunocompromised children, a full course of TPT should be initiated right after excluding tuberculosis, irrespective of the TBI test result.

Window prophylaxis is the practice of treating contacts of TB cases with TPT during the early phase when the TBI test may not yet be positive. Window prophylaxis prevents rapid progression to tuberculosis soon after infection.

4.1.2.b. People living with HIV

- If testing positive for TB infection: give TPT.
- If testing negative for TB infection: no need to provide TPT unless the PLHIV is a contact of a contagious TB case (see 3.1.4.c). A full course of TPT is to be given, irrespective of the result if repeat testing is performed 2-3 months later.
- If TST and IGRA results are discordant: Consider TPT if one of the tests is positive and a high risk for TB is present (see table 1).

4.1.2.c. Pregnancy, postpartum and lactation

- Pregnancy increases the risk of progression to tuberculosis and, should the disease occurs, there is a risk of poor maternal and foetal outcomes. Pregnancy does not disqualify women from receiving TPT (5).
- Consider immediate TPT, after tuberculosis is excluded, if the woman is HIV infected or has a recent contact and monitor.
- Breastfeeding is not contraindicated in women taking (non-MDR) TPT.
- Approximately 3 % of the maternal dose is secreted in the breastmilk. The amount of INH in breast milk is inadequate for TPT of newborn/infants with TBI.

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

As with other forms of TB infection, the benefit of TPT must be weighed against the risk of drug toxicity, non-adherence and the possibility that the fibrotic lesions may be tuberculosis. 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) (38). In general, younger age indicates a higher risk of reactivation and tuberculosis should be excluded. If no tuberculosis is detected, start TPT. With increasing age, the risk of reactivation decreases, but the probability of adverse drug effects increases. The treating physician should weigh the risk of TPT against the extent of the lesions.

4.1.3. Preventive treatment for contacts of multidrug-resistant tuberculosis cases

WHO recommends 6 months of levofloxacin as a TPT option for people exposed to MDR tuberculosis (5). Levofloxacin is the preferred choice of fluoroquinolone over moxifloxacin. Before initiating the 6 months levofloxacin regimen:

- Rule out active TB disease
- Weight benefits and risks of TPT, taking into account age, toxicity or interactions, co-morbidities...
- Exclude a fluoroquinolone resistance in the index case.

In case the index case is pre-XDR, or levofloxacin is not an option, contact the Belta-TB expert group for an alternative regimen[9].

9 info@belta.be

4.2. TREATMENT REGIMENS FOR TB PREVENTIVE TREATMENT

4.2.1. General considerations

Several possible treatment regimens are recommended by WHO (5).

The combination of INH + rifapentine (P) is not available in Belgium [10].

For people exposed to drug-sensitive tuberculosis, WHO recommends broadly 2 categories of preventive treatment: the RMP-based shorter regimens (3 RH and 4 R) and the INH monotherapy regimen (6 H) (5).

The comparative evidence for those 2 categories of TPT regimens comes from meta-analyses conducted in 2014 (69) and updated in 2017 (70). These analyses found no clear superiority of any particular regimen in terms of efficacy, though the data was limited by few direct comparisons between treatments. While 3-4 month RMP regimens showed fewer hepatotoxicity events compared to 6-9 month INH regimens, the quality of evidence was considered low. However, one significant advantage of RMP-based regimens is the documented 20 % better treatment completion rate, likely due to the shorter duration of treatment.

It's important to consider RMP's drug interaction profile. RMP strongly induces multiple metabolic pathways, particularly affecting cytochrome P450 enzymes (CYP3A4, CYP2C9, CYP2C19, and CYP1A2) and UDP-glucuronosyltransferases (UGTs). These interactions can substantially reduce the effectiveness of many concurrent medications. This is relevant for specific patient groups, such as those on oral contraceptives or antiretroviral therapy, where these interactions can significantly impact treatment choices. For pregnant patients, while both RMP and INH can be used, there are specific risks to consider, including increased hepatotoxicity with each of these drugs and potential thrombocytopenia with late-pregnancy RMP use.

The combination of RMP and PZA has been abandoned in the face of the higher hepatotoxicity (71) (72) (73).

4.2.2. TPT regimens recommended in Belgium

Since May 1, 2024, treatment with RMP has been reimbursed in Belgium for TB infection under the same conditions as for tuberculosis (https://www.cbip.be/fr/ampps/3301?cat=a).

Therefore, both shorter RMP based regimens and the INH monotherapy regimen are available for preventive treatment and are now all covered by the national health security.

10 Rifapentine, a rifamycin with a serum half-life five times that of RMP, either weekly dosing during 3 months (3 HP) or daily dosing during 1 month (1 HP) (102), could have an added value, especially the 1 HP regimen, because of its short duration. However, the 1 HP regimen requires more evidence to support its universal use.

When selecting appropriate treatment options, clinicians should consider the characteristics of individual patients in need of TPT 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 TPT regimens recommended in Belgium are shown in table 9:

Table 9. TPT regimens recommended in Belgium

Regimen	Indication
3RH (daily RMP and INH during 3 months)	Recommended for all Highly recommended in children
4R (RMP daily during 4 months)	E.g., if the strain of the index case is known to be INH resistant or for young children whom administration of 2 drugs rather than one might be an issue[10]
6H (INH daily during 6 months)	If the index case is mono resistant to RMP To avoid RMP's drug interactions, e.g. with oral contraceptives
6 months of levofloxacin	When the index case is known to be MDR and fluoroquinolone resistance is excluded

Table 10 gives the recommended doses of INH, RMP and levofloxacin. INH and RMP 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)[12] under 11.1.8.1 (isoniazid), 11.1.8.2 (rifampicin) and 11.1.5 (levofloxacin).

Table 10. Recommended treatment dosing (9)

Drug	Dose per body weight		Maximum dose
	Child	Adult	
Daily INH	10 mg/kg (range 7-15 mg)[12]	5 mg/kg	300 mg
Daily RMP	15 mg/kg (range 10-20 mg)	10 mg/kg	600 mg
Daily levofloxacine	Range 15-20 mg/kg/day 5–9 kg: 150 mg/day; 10–15 kg: 200-300 mg/day; 16–23 kg: 300-400 mg/day; 24–34 kg: 500-750 mg/day	< 46 kg: 750 mg ≥ 46 kg: 1 g	1 g

11 Dispersible RH Fixed Drug Combinations are not available in Belgium.

12 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)

13 Some guidelines (MMWR) suggest the possibility to go up to 20 mg/kg.

Dosages are the same for both mono- and bi-therapy. Give on an empty stomach.

In children, dosing must be adapted regularly according to changing weight. Magistral preparations in capsules are preferred over syrups. The capsule contents can be mixed with a small amount of soft food that is low in fat or dairy (e.g., applesauce).

4.2.3. For specific patients

4.1.2.a. Woman and pregnancy

- RMP should NOT be used in women deciding to continue with oral contraceptives after being informed.
- During pregnancy and post-partum:
  - Both RMP-based and INH regimens can be prescribed
  - Close monitoring for hepatotoxicity is required
- If using RMP late in pregnancy:
  - Give vitamin K to mother and child post-partum to reduce haemorrhage risk

4.1.2.b. HIV patients

- If INH cannot be used, seek expert advice about alternative antiretroviral regimens
- Use RMP-containing regimens with caution in patients on antiretroviral therapy: always check interactions (Liverpool HIV Interactions website: https://www.hiv-druginteractions.org/)

4.1.2.c. When INH treatment is prescribed

Vitamin B6 (pyridoxine) supplementation at 2mg/kg/day is recommended for specific groups:
- Pregnant women
- Breastfed children
- Insufficient diet
- Adolescents
- Alcoholism

Since pyridoxine alone is no longer available in Belgium, Befact®, which includes 250 mg of B6 along with other vitamins, is now used.
- For adults: 1 co per week
- For children from 1 to 12 years old: ½ co per week
- For children < 1 year old: ¼ co per week.

4.3. BEFORE STARTING TPT

Before starting any TPT, tuberculosis disease [14] must be ruled out, particularly if fibrotic lesions are seen on the chest X-ray. A clinical workup, including clinical assessment of symptoms and signs of tuberculosis (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 pulmonary or extra-pulmonary tuberculosis.

Do not initiate TPT in children presenting with symptoms compatible with tuberculosis (e.g., fever, weight loss /poor weight gain, etc.) without first conducting a comprehensive workup to rule TB (especially extrapulmonary TB), such as visceral lymphadenopathy or meningitis.

It is important that this testing is done before any TPT is initiated, to avoid development of resistance in a patient that might have tuberculosis. If these exams do not show active tuberculosis, TPT can be initiated if the patient will adhere to treatment and the risk of developing tuberculosis outweighs the risk of TPT drugs toxicity.

When evaluating patient's adherence, it is important to consider the benefit of therapy versus the risk of emerging resistance if tuberculosis were to develop during inadequate TPT (4). A risk analysis evaluating the likelihood of non-compliance should be performed. If the patient is considered to be at high risk for developing tuberculosis but there are concerns about their compliance, a short regimen under DOT should be considered.

Contra-indications to TPT must be excluded, such as hypersensitivity to the treatment regimen and severe hepatic failure. Baseline laboratory testing for measurements of liver enzymes and bilirubin is certainly 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 (74)
- 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).

Prior to initiating INH-based treatment, it is advisable to assess the G6PD activity if there is a potential concern for G6PD deficiency (75).

If the drug sensitivity testing result of the index case is known, check whether the strain is susceptible to INH and RMP.

14 Diagnosis and treatment of tuberculosis in Belgium. Recommendations for physicians.
https://tuberculose.vrgt.be/sites/default/files/VRGT%20-%20Diagnose%20en%20behandeling%20van%20tuberculose%20een%20praktische%20handleiding%20voor%20artsen.pdf (flemish)
https://fares.devexp.be/documentation/tuberculose (french)

4.4. FOLLOW-UP DURING TREATMENT

4.4.1. Routine monitoring

Regular clinical monitoring of individuals receiving TPT through a monthly visit to healthcare providers is of importance to exclude tuberculosis, ensure therapeutic compliance and detect adverse drug reactions.

The prescribing health care provider should clearly explain the rationale for the TPT and stress the importance of completing the full course. Those receiving TPT should be instructed to contact their healthcare providers in case they develop symptoms such as paraesthesia, anorexia, nausea, vomiting, abdominal discomfort, persistent fatigue or weakness, dark coloured urine, pale stools or jaundice.

The clinician must also monitor for drug side effects, such as neurotoxicity and hepatotoxicity, and conduct a clinical evaluation to rule out the development of tuberculosis if suggestive symptoms arise during TPT.

Monthly blood checks are recommended 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.

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) (76).

Determinants of TPT initiation, adherence and completion identified in a systematic review (76) were: 1) adverse drug reactions, 2) longer duration of treatment, 3) long distance from health facility, 4) history of incarceration, 5) absence of perception of risk, 6) presence of stigma, 7) alcohol and drug use, 8) unemployment, and 9) time lag between diagnosis and TPT.

Evidence on the efficacy of interventions to improve TPT adherence and completion showed that shorter treatment duration was significantly associated with increased adherence. Significantly better completion rates were demonstrated with peer support and coaching among adolescents and adults, nurse case management for homeless people, cultural case management for immigrants and educational interventions for inmates.

The evidence regarding the most appropriate interventions to improve TPT adherence and completion is heterogeneous and inconclusive. Techniques that may improve adherence include: patient education and instructions in the patient's primary language at every visit, nurse confidentiality, patient reminders such as pill box, calendar, or timer. Economic incentives and linking a person to social services may also increase adherence. Eventually, consider directly

observed therapy if patient is at high risk (e.g., HIV-infected or TB contact) and at risk of non-compliance.

Patients who interrupt or fail to complete TPT should be encouraged to finish it. Table 11 shows whether the original regimen should be continued or a new course of TPT should be initiated. This will depend on when the interruption occurs, the duration of the interruption and the number of doses lost.

Restarting TPT means initiating a new course of the initial regimen. The duration of the new course will be of the same as that of the initial one. A prolonged regimen is not necessary. Before starting the new course of TPT, tuberculosis must again be ruled out.

Table 11. Criteria to continue the initial regimen or to start a new regimen in case of TPT interruption (5)

Duration of interruption			
< 2 weeks	Resume TPT and add the missing doses in order to complete the total number of doses		
≥ 2 weeks	**% doses already taken when the interruption occurs**		
	≥ 80 %	< 80 %	
	Resume TPT and add the missing doses in order to complete the total number of doses	If the TPT can still be completed within the acceptable maximum deadline*,resume TPT and add the missing doses in order to complete the number of doses	If the TPT cannot be completed within the acceptable maximum deadline*, restart TPT

* Acceptable maximum deadline = TPT duration + 33 % of the TPT duration.
Ex. For 6H, the acceptable maximum deadline is 6 months +2 months = 8 months

If a patient has failed three attempts to complete the TPT, 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) (77) (78). 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 postpartum, excessive alcohol consumption or an active intravenous drug user (79).

It is recommended to withhold TPT 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 for asymptomatic patients.

In people who have experienced an interruption in TPT because of drug-induced hepatotoxicity: consider stopping the TPT after a careful risk/benefit assessment. If continuation of TPT is preferred, investigate other causes of acute liver reactions and wait until transaminase levels fall below twice the upper limit of normal and hepatotoxic symptoms have resolved (5). However, the clinician must balance risk and benefits if TPT is deemed to be the cause of the hepatotoxicity. TPT may be stopped if the risk of severe hepatotoxicity is considered unacceptably high, but TPT based on RMP monotherapy would be a valid alternative (69).

4.5.1.b. Peripheral neuropathy

Peripheral neuropathy 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". Vitamin B6 (Befact) supplementation is recommended only in such conditions or to prevent neuropathy in pregnant or breastfeeding women, in children being breastfed and in adolescents (5) (80) (81) (82).

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 like RMP 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 informed before starting TPT. Soft contact lenses and dentures may be permanently stained.

4.5.3. Levofloxacin

The ongoing studies showed an important difference in the occurrence of adverse events between children and adults, with a very good tolerance among children (5) (84). The most commonly observed adverse events are dizziness, headache, nausea and abdominal pain but these rarely require discontinuation of the therapy. Fluoroquinolones can also cause arthralgia and a risk of tendinopathy which increases with age and concomitant corticosteroid therapy. As levofloxacin might affect glucose metabolism, blood sugar levels should be monitored.

4.5.4. 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 (85). 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 considered 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 TPT HAS BEEN COMPLETED

Patients should be counselled to contact their treating physician if possible symptoms of tuberculosis 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 repeating the test is unnecessary once it is positive.

In the case of re-exposure, a new TB infection can always occur; previous exposure does not protect against re-infection. Advise from an expert physician should be sought.

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

ANNEXES

Annex 1. The tuberculin skin test (TST)

A1.1. 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 (54) (86), comparative studies show variations between the formulations regarding the relative abundance of several proteins that could influence test results (87). 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 72h, 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.

A1.2. Execution of the TST

Normally, only 1 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: 0.1ml 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 (88).

A1.3. 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 24h after injection without the apparition of an induration beyond 48h 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 (78) (89). 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 (90). A vaso-vagal reaction is not a contra-indication for future administration of TST.

Annex 2. The IGRA tests

A2.1. Principle of IGRA tests

IGRA 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 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.

A2.2. 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

A2.2.1. 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	$CD8^+$ cells
QuantiFERON Mitogen Tube	Violet	Positive control

A2.2.2. Execution of the test

Whole blood is collected into the four tubes (1ml 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.

A2.2.3. 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

<table>
<tr><th>Nil (IU/ml)</th><th>TB1 minus Nil (IU/ml)</th><th>TB2 minus Nil (IU/ml)</th><th>Mitogen minus Nil (IU/ml)</th><th>QFT®-Plus Result</th><th>Report/Interpretation</th></tr>
<tr><td rowspan="4">≤ 8.0</td><td>≥ 0.35 and ≥ 25 % of Nil</td><td>Any</td><td rowspan="2">Any</td><td rowspan="2">Positive</td><td rowspan="2">M. tuberculosis infection likely</td></tr>
<tr><td>Any</td><td>≥ 0.35 and ≥ 25 % of Nil</td></tr>
<tr><td colspan="2" rowspan="2">< 0.35
OR
≥ 0.35 and < 25 % of Nil</td><td>≥ 0.5</td><td>Negative</td><td>M. tuberculosis infection NOT likely</td></tr>
<tr><td>< 0.5</td><td rowspan="2">Indeterminate</td><td rowspan="2">Likelihood of M. tuberculosis infection cannot be determined</td></tr>
<tr><td>> 8.0</td><td colspan="3">Any</td></tr>
</table>

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 effected.

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 (91).

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.

A2.3. 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.

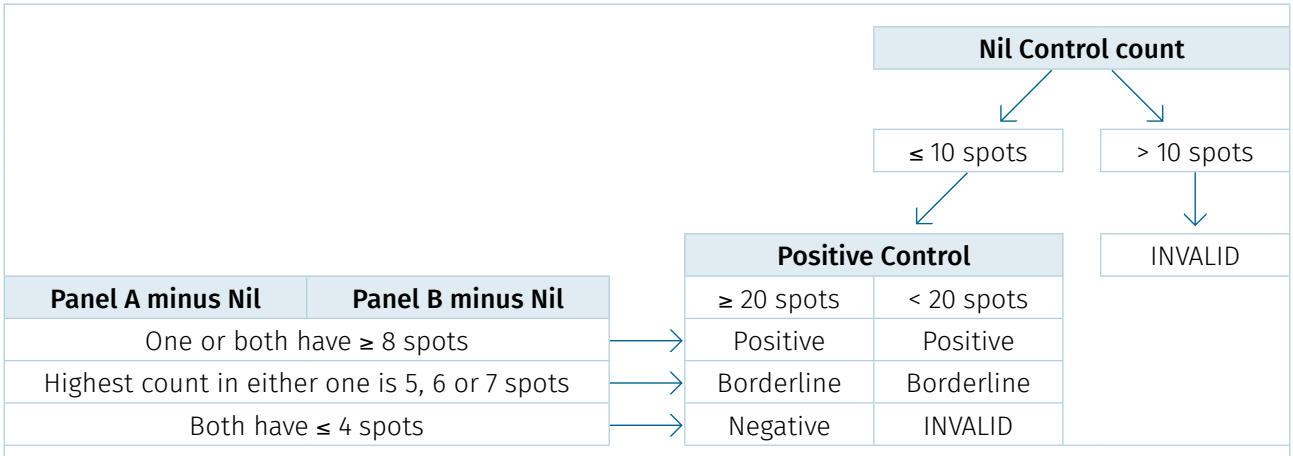


Figure A1. Interpretation of the T-SPOT®.TB results

A2.4. 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.

REFERENCES

1. VRGT/FARES. Gerichte Opsporing en Behandling van Latente Tuberculose-Infectie (2003).
2. WHO. *Guidelines on the Management of Latent Tuberculosis Infection*. World Health Organization; 2015. https://www.who.int/publications/i/item/9789241548908
3. Getahun H, Matteelli A, Abubakar I, et al. Management of latent Mycobacterium tuberculosis infection: WHO guidelines for low tuberculosis burden countries. *Eur Respir J*. 2015:ERJ-01245-2015. doi:10.1183/13993003.01245-2015
4. NICE. *Tuberculosis NICE Guidelines*.; 2016. https://www.nice.org.uk/guidance/NG33
5. WHO consolidated guidelines on tuberculosis. Module 1: Prevention - Tuberculosis preventive treatment, 2nd edition. Geneva: World Health Organization; 2024. WHO consolidated guidelines on tuberculosis: tuberculosis preventive treatment. https://iris.who.int/bitstream/handle/10665/378535/9789240097773-eng.pdf?sequence=1
6. WHO. Towards tuberculosis elimination: an action framework for low-incidence countries. WHO/HTM/TB/2014.13. World Health Organization, Geneva, 2014. https://www.who.int/publications/i/item/9789241507707
7. WHO. *Global Strategy and Targets for Tuberculosis Prevention, Care and Control after 2015*.; 2015. http://apps.who.int/gb/ebwha/pdf_files/EB134/B134_12-en.pdf?ua=1
8. Houben RM, Dodd PJ. The global burden of latent tuberculosis infection: a re-estimation using mathematical modelling. *PLoS Med* 2016;13:e1002152. doi:10.1371/journal.pmed.1002152 pmid:27780211
9. Behr Marcel A, Edelstein Paul H, Ramakrishnan Lalita. Revisiting the timetable of tuberculosis *BMJ* 2018;362:k2738 https://www.bmj.com/content/362/bmj.k2738
10. Comstock GW, Livesay VT, Woolpert SF. The prognosis of a positive tuberculin reaction in childhood and adolescence. *Am J Epidemiol*. 1974;99(2):131-138. http://www.ncbi.nlm.nih.gov/pubmed/4810628
11. Borgdorff MW, Sebek M, Geskus RB, Kremer K, Kalisvaart N, van Soolingen D. The incubation period distribution of tuberculosis estimated with a molecular epidemiological approach. *Int J Epidemiol*. 2011;40(4):964-970. doi:10.1093/ije/dyr058
12. Esmail H, Barry CE, Young DB, Wilkinson RJ. The ongoing challenge of latent tuberculosis. *Philos Trans R Soc B Biol Sci*. 2014;369(1645):20130437-20130437. doi:10.1098/rstb.2013.0437
13. Getahun H, Matteelli A, Chaisson RE, Raviglione M. Latent Mycobacterium tuberculosis Infection. N *Engl J Med*. 2015;372(22):2127-2135. doi:10.1056/NEJMra1405427
14. The HIV-CAUSAL Collaboration. Impact of Antiretroviral Therapy on Tuberculosis Incidence Among HIV-Positive Patients in High-Income Countries. *Clin Infect Dis*. 2012;54(9):1364-1372. doi:10.1093/cid/cis203
15. Lodi S, del Amo J, d'Arminio Monforte A, et al. Risk of tuberculosis following HIV seroconversion in high-income countries. *Thorax*. 2013;68(3):207-213. doi:10.1136/thoraxjnl-2012-201740
16. Akolo C, Adetifa I, Shepperd S, Volmink J. Treatment of latent tuberculosis infection in HIV infected persons. *Cochrane database Syst Rev*. 2010;(1):CD000171. doi:10.1002/14651858.CD000171.pub3

17. Lobue P, Menzies D. Treatment of latent tuberculosis infection: An update. *Respirology*. 2010;15(4):603-622. doi:10.1111/j.1440-1843.2010.01751.x

18. Alsdurf H, Hill PC, Matteelli A, Getahun H, Menzies D. The cascade of care in diagnosis and treatment of latent tuberculosis infection: a systematic review and meta-analysis. *Lancet Infect Dis*. 2016;16(11):1269-1278. doi:10.1016/S1473-3099(16)30216-X

19. Erkens CGM, Kamphorst M, Abubakar I, et al. Tuberculosis contact investigation in low prevalence countries: a European consensus. *Eur Respir J*. 2010;36(4):925-949. doi:10.1183/09031936.00201609

20. Government of Canada Public Health Agency of Canada. Canadian Tuberculosis Standards. 7th Edition 2014 - Chapter 4: Diagnosis of Latent Tuberculosis Infection. https://www.canada.ca/en/public-health/services/infectious-diseases/canadian-tuberculosis-standards-7th-edition.html

21. Marais BJ, Gie RP, Schaaf HS, et al. The natural history of childhood intra-thoracic tuberculosis: a critical review of literature from the pre-chemotherapy era. *Int J Tuberc Lung Dis*. 8(4) 2004, 392-402.

22. European Centre for Disease Prevention and Control. Programmatic management of latent tuberculosis infection in the European Union. Stockholm: ECDC, October 2018. ISBN 978-92-9498-266-7.

23. Chloé Wyndham-Thomas, Violette Dirix, Jean-Christophe Goffard, Sophie Henrard, Maryse Wanlin, Steven Callens, Françoise Mascart & Jean-Paul Van Vooren (2018). 2018 Belgian guidelines for the screening for latent tuberculosis in HIV-infected patients. *Acta Clinica Belgica*. https://doi.org/10.1080/17843286.2018.1494669

24. WHO. *Recommendations for Investigating Contacts of Persons with Infectious Tuberculosis in Low- and Middle-Income Countries*.; WHO/HTM/TB/2012.9. World Health Organization, Geneva, 2012. https://www.who.int/publications/i/item/9789241504492

25. Chuke SO. Tuberculin Skin Tests versus Interferon-Gamma Release Assays in Tuberculosis Screening among Immigrant Visa Applicants. *Tuberc Res Treat*. 2014; 2014:217969.

26. Seddon JA, Paton J, Nademi Z, et al. The impact of BCG vaccination on tuberculin skin test responses in children is age dependent: evidence to be considered when screening children for tuberculosis infection. *Thorax*. 2016;71(10):932-939. doi:10.1136/thoraxjnl-2015-207687

27. Berti E, Galli L, Venturini E, et al. Tuberculosis in childhood: a systematic review of national and international guidelines. *BMC Infect Dis* 2014;14.

28. WHO. Guidance for national tuberculosis programme on the management of tuberculosis in children (second edition). World Health Organization, Geneva 2014. https://www.who.int/publications/i/item/9789241548748

29. Malhamé I, Cormier M, Sugarman J, Schwartzman K. Latent Tuberculosis in Pregnancy: A Systematic Review. Manganelli R, ed. *PLoS One*. 2016;11(5):e0154825. doi:10.1371/journal.pone.0154825

30. Advies van de Hoge Gezondheidsraad Nr 8579: Aanbevelingen Betreffende de Preventie van Tuberculose in Zorginstellingen (Belgian Superior Health Council. Science - policy advisory report. Recommendations regarding the prevention of tuberculosis in healthcare facilities). Update 2/07/2014. https://www.health.belgium.be/sites/default/files/uploads/fields/fpshealth_theme_file/19091280/Aanbevelingen %20betreffende %20de %20preventie %20van %20tuberculose %20 %28november %202013 %29 %20 %28HGR %208579 %29.pdf

31. Redelman-Sidi G, Sepkowitz KA. IFN-γ Release Assays in the Diagnosis of Latent Tuberculosis Infection among Immunocompromised Adults. *Am J Respir Crit Care Med*. 2013;188(4):422-431. doi:10.1164/rccm.201209-1621CI

32. Rangaka MX, Wilkinson RJ, Boulle A, et al. Isoniazid plus antiretroviral therapy to prevent tuberculosis: a randomised double-blind, placebo-controlled trial. *Lancet*. 2014;384(9944):682-690. doi:10.1016/S0140-6736(14)60162-8

33. The TEMPRANO ANRS 12136 Study group. A Trial of Early Antiretrovirals and Isoniazid Preventive Therapy in Africa. *N Engl J Med.* 2015;373(9):808-822. doi:10.1056/NEJMoa1507198

34. Getahun H, Granich R, Sculier D, et al. Implementation of isoniazid preventive therapy for people living with HIV worldwide: barriers and solutions. *AIDS*. 2010;24(Suppl 5):S57-S65. doi:10.1097/01.aids.0000391023.03037.1f

35. Solsona Peiró J, de Souza Galvão ML, Altet Gómez MN. Inactive Fibrotic Lesions Versus Pulmonary Tuberculosis With Negative Bacteriology. *Arch Bronconeumol* (English Ed.) 2014;50(11):484-489. https://www.archbronconeumol.org/en-inactive-fibrotic-lesions-versus-pulmonary-articulo-S1579212914002523

36. Ferebee SH. Controlled chemoprophylaxis trials in tuberculosis. A general review. *Bibl Tuberc*. 1970;26:28-106. http://www.ncbi.nlm.nih.gov/pubmed/4903501

37. Jenkins D, Davidson FF. Isoniazid chemoprophylaxis of tuberculosis. *Calif Med*. 1972;116(4):1-5. http://www.ncbi.nlm.nih.gov/pubmed/5019090

38. Diagnostic Standards and Classification of Tuberculosis in Adults and Children. *Am J Respir Crit Care Med.* 2000;161(4):1376-1395. https://www.atsjournals.org/doi/abs/10.1164/ajrccm.161.4.16141#readcube-epdf

39. Diel R, Loddenkemper R, Meywald-Walter K, Niemann S, Nienhaus A. Predictive value of a whole blood IFN-gamma assay for the development of active tuberculosis disease after recent infection with Mycobacterium tuberculosis. *Am J Respir Crit Care Med*. 2008;177(10):1164-1170. doi:10.1164/rccm.200711-1613OC

40. Bottieau E, Van Gompel A. Bilan de Santé chez le voyageur asymptomatique de retour des tropiques. *Rev Med Suisse*. 2009;5:1016-1021.

41. Denholm JT, Thevarajan I. Tuberculosis and the traveller: evaluating and reducing risk through travel consultation. *J Travel Med*. 2016;23(3). http://www.ncbi.nlm.nih.gov/pubmed/27358971

42. Erkens CGM, Dinmohamed AG, Kamphorst M, et al. Added value of interferon-gamma release assays in screening for tuberculous infection in the Netherlands. *Int J Tuberc Lung Dis*. 2014;18(4):413-420. doi:10.5588/ijtld.13.0589

43. Ruan Q, Zhang S, Ai J, Shao L, Zhang W. Screening of latent tuberculosis infection by interferon-γ release assays in rheumatic patients: a systemic review and meta-analysis. *Clin Rheumatol* 2016; 35(2): 417–425.

44. Pai M, Denkinger CM, Kik S V., et al. Gamma Interferon Release Assays for Detection of Mycobacterium tuberculosis Infection. *Clin Microbiol Rev*. 2014;27(1):3-20. doi:10.1128/CMR.00034-13

45. Pai M, Kalantri S, Dheda K. New tools and emerging technologies for the diagnosis of tuberculosis: Part I. Latent tuberculosis. *Expert Rev Mol Diagn*. 2006;6(3):413-422. doi:10.1586/14737159.6.3.413

46. Mandalakas AM. Interferon-gamma release assays and childhood tuberculosis: systematic review and meta-analysis. *Int J Tuberc Lung Dis*. 201.1

47. Machingaidze S. The utility of an interferon gamma release assay for diagnosis of latent tuberculosis infection and disease in children: a systematic review and meta-analysis. *Pediatr Infect Dis J*. 2011.

48. Sun L, Xiao J, Miao Q, et al. Interferon gamma release assay in diagnosis of pediatric tuberculosis: a meta-analysis. *FEMS Immunol Med Microbiol*. 63 (2011) 165–173.

49. Starke JR; Committee On Infectious Diseases. Interferon-γ release assays for diagnosis of tuberculosis infection and disease in children. *Pediatrics*. 2014 Dec;134(6):e1763-73.

50. Doan TN, Eisen DP et al. Interferon-gamma release assay for the diagnosis of latent tuberculosis infection: a latent-class analysis. *Plos One* 2017 Nov. 28; 12 (11). doi: 10.1371/journal.pone.0188631

51. Lewinsohn DM, et al. Official American Thoracic Society/Infectious Diseases Society of America/Centers for Disease Control and Prevention Clinical Practice Guidelines: Diagnosis of Tuberculosis in Adults and Children. *Clin Infect Dis*. 2017 Jan 15;64(2):111-115.

52. Velasco-Arnaiz E, Soriano-Arandes A et al. Performance of tuberculin skin tests and interferon-γ release assays in children younger than 5 years. *The Pediatric Infectious Disease Journal*. 37(12):1235-12412, December 2018.

53. O'Shea MK, Fletcher TE, Beeching NJ, et al. Tuberculin skin testing and treatment modulates interferon-gamma release assay results for latent tuberculosis in migrants. *PLoS One*. 2014;9(5):1-11. doi:10.1371/journal.pone.0097366

54. Guld J, Bentzon MW, Bleiker MA. Standardization of a new batch of purified tuberculin (PPD) intended for international use. Bull WHO. 1958;19:845-951.

55. Centers for Disease Control and Prevention (CDC). Tuberculosis Fact Sheets. Tuberculin Skin Testing. https://www.cdc.gov/tb/publications/factsheets/testing/Tuberculin_Skin_Testing_Information_for_Health_Care_Providers.pdf

56. Diel R, Nienhaus A. [Current Issues Arising from Tuberculosis Screening with Interferon-Gamma-Release Assays (IGRAs)]. *Pneumologie*. 2015;69(5):271-275. doi:10.1055/s-0034-1391919

57. Farhat M, Greenaway C, Pai M, Menzies D. False-positive tuberculin skin tests: what is the absolute effect of BCG and non-tuberculous mycobacteria? *Int J Tuberc Lung Dis*. 2006;10(11):1192-1204. http://www.ncbi.nlm.nih.gov/pubmed/17131776

58. Waddell RD, Von Reyn CF, Baboo KS, et al. The effects of BCG immunization and human immunodeficiency virus infection on dual skin test reactions to purified protein derivative and mycobacterium avium sensitin among adults in Zambia. *Int J Tuberc Lung Dis* 1999; 3(3), 255-260.

59. American Academy of Pediatrics. Tuberculosis. In: Pickering LK, Baker CJ, Kimberlin DW, Long SS, eds. Red Book: 2012 Report of the Committee on Infectious Diseases. Elk Grove Village, IL: American Academy of Pediatrics; 2012:736–759.

60. Red Book 2018. Committee on Infectious Diseases; American Academy of Pediatrics; Kimberlin DW, Brady MT, Jackson MA, Long SS (editors). https://redbook.solutions.aap.org/book.aspx?bookid=2205

61. Menzies D. Interpretation of repeated tuberculin tests. Boosting, conversion and reversion. *Am J Respir Crit Care Med.* (159) 1999, 15-21. http://www.atsjournals.org/doi/full/10.1164/ajrccm.159.1.9801120

62. Battershill JH. Cutaneous Testing in the Elderly Patient with Tuberculosis. *Chest*. 1980;77(2):188-189. doi:10.1378/chest.77.2.188

63. Van den Brande P, Demedts M. Four-stage tuberculin testing in elderly subjects induces age dependent progressive boosting. *Chest*. 1992;101(2):447-50.

64. Banaei N, Pai M. Editorial. Detecting new Mycobacterium tuberculosis infection. Time for a more nuanced Interpretation of QuantiFERON conversions. *Am J Respir Crit Care Med.* (196) 2017, 546-547. http://www.atsjournals.org/doi/10.1164/rccm.201707-1543ED

65. van Zyl-Smit RN, Zwerling A, Dheda K, Pai M. Within-subject variability of interferon-g assay results for tuberculosis and boosting effect of tuberculin skin testing: a systematic review. *PLoS One*. 2009;4(12):e8517. doi:10.1371/journal.pone.0008517

66. Song GG, Bae S-C, Lee YH. Interferon-gamma release assays versus tuberculin skin testing in patients with rheumatoid arthritis. *Int J Rheum Dis*. 2013;16(3):279-283. doi:10.1111/1756-185X.12098

67. Ismail S, Crowcroft N, Hanrahan A, et al. Recommendations on Interferon Gamma Release Assays for the Diagnosis of Latent Tuberculosis Infection - 2010 Update. October. 2010;35(September):1-41.

68. Village G. Targeted Tuberculin Skin Testing and Treatment of Latent Tuberculosis Infection in Children and Adolescents. *Pediatrics*. 2004;114(4):1175-1201. doi:10.1542/peds.2004-0809

69. Stagg HR, Zenner D, Harris RJ, et al. Treatment of latent tuberculosis infection: a network meta-analysis. *Ann Intern Med.* 2014; 161: 419–428.

70. Zenner D, Beer N, Harris RJ, Lipman MC, Stagg HR, van der Werf MJ. Treatment of latent tuberculosis infection: An updated network meta-analysis. *Ann Intern Med.* 2017;167(4):248–55.

71. McNeill L, Allen M, Estrada C, Cook P. Pyrazinamide and Rifampin vs Isoniazid for the Treatment of Latent Tuberculosis. *Chest*. 2003;123(1):102-106. doi:10.1378/chest.123.1.102.

72. Schechter M, Zajdenverg R, Falco G, et al. Weekly Rifapentine/Isoniazid or Daily Rifampin/Pyrazinamide for Latent Tuberculosis in Household Contacts. *Am J Respir Crit Care Med*. 2006;173(8):922-926. doi:10.1164/rccm.200512-1953OC

73. Sharma SK, Sharma A, Kadhiravan T, Tharyan P. Rifamycins (rifampicin, rifabutin and rifapentine) compared to isoniazid for preventing tuberculosis in HIV-negative people at risk of active TB. In: Sharma SK, ed. Cochrane Database of Systematic Reviews. Chichester, UK: John Wiley & Sons, Ltd; 2013. doi:10.1002/14651858.CD007545.pub2

74. Kunst H1, Khan KS. Age-related risk of hepatotoxicity in the treatment of latent tuberculosis infection: a systematic review. *Int J Tuberc Lung Dis*. 2010 Nov;14(11):1374-81.

75. Bubp J, Jen M, Matuszewski K. Caring for Glucose-6-Phosphate Dehydrogenase (G6PD)–Deficient Patients: Implications for Pharmacy. *Pharmacy & Therapeutics*. 2015 Sep; 40(9): 572–574.

76. Hirsch-Moverman Y, Daftary A, Franks J, Colson PW. Adherence to treatment for latent tuberculosis infection: systematic review of studies in the US and Canada. *Int J Tuberc Lung Dis*. 2008;12(11):1235-1254. http://www.ncbi.nlm.nih.gov/pubmed/18926033

77. Centers for Disease Control and Prevention (CDC). Latent Tuberculosis Infection: A Guide for Primary Health Care Providers.; 2013. https://www.cdc.gov/tb/hcp/education/latent-tb-infection-guide-primary-care-providers.html

78. Youssef E. Serious allergic reactions following tuberculin skin tests. *Can Med Assoc J*. 2005;173(1):34-34. doi:10.1503/cmaj.050710

79. Gray EL, Goldberg HF. Baseline abnormal liver function tests are more important than age in the development of isoniazid-induced hepatoxicity for patients receiving preventive therapy for latent tuberculosis infection. *Intern Med J*. 2016;46(3):281-287. doi:10.1111/imj.12979

80. Targeted Tuberculin Testing and Treatment of Latent Tuberculosis Infection. *Am J Respir Crit Care Med*. 2000;161(supplement_3):S221-S247. https://www.atsjournals.org/doi/full/10.1164/ajrccm.161.supplement_3.ats600#readcube-epdf

81. Mbala L, Matendo R, Nkailu R. Is vitamin B6 supplementation of isoniazid therapy useful in childhood tuberculosis. *Trop Doct*. 1998;28(2):103-104. http://www.ncbi.nlm.nih.gov/pubmed/9594683

82. Rodà D, Rozas L, Fortuny C, Sierra C, Noguera-Julian A. Impact of the Increased Recommended Dosage of Isoniazid on Pyridoxine Levels in Children and Adolescents. *Pediatr Infect Dis J*. 2016;35(5):586-589. doi:10.1097/INF.0000000000001084

83. Menzies D, Adjobimey M, Ruslami R et al. Four Months of Rifampin or Nine Months of Isoniazid for Latent Tuberculosis in Adults. *N Engl J Med* 2018;379:440-53. DOI: 10.1056/NEJMoa1714283

84. Duong T, Brigden J, Schaaf S et al. A Meta-Analysis of Levofloxacine for Contacts of Multdrug-Resistant Tuberculosis. *N Engl J Med Evid* 2024; 4(1). A Meta-Analysis of Levofloxacin for Contacts of Multidrug-Resistant Tuberculosis | NEJM Evidence https://evidence.nejm.org/doi/10.1056/EVIDoa2400190?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub %20 %200pubmed

85. Niemi M, Backman JT, Fromm MF, Neuvonen PJ, Kivist KT. Pharmacokinetic Interactions with Rifampicin. Clinical Relevance. *Clin Pharmacokinet*. 2003; 42 (9): 819-850.

86. Sagebiel D, Magdorf K, Loddenkemper R. WHO-Recommended Tuberculin PPD RT23 SSI Now Approved in Germany. *Pneumologie*. 2005;59(11):761-762. doi:10.1055/s-2005-915638

87. Yang H, Kruh-Garcia NA, Dobos KM. Purified protein derivatives of tuberculin — past, present, and future. *FEMS Immunol Med Microbiol*. 2012;66(3):273-280. doi:10.1111/j.1574-695X.2012.01002.x

88. Caminero Luna JA. A tuberculosis guide for specialist physicians. International Union against Tuberculosis and Lung Diseases. Paris, 2003. P 57-59. https://tbrieder.org/publications/books_english/specialists_en.pdf

89. Froeschle JE, Ruben FL, Bloh AM. Immediate Hypersensitivity Reactions after Use of Tuberculin Skin Testing. *Clin Infect Dis*. 2002;34(1):e12-e13. doi:10.1086/324587

90. Mahajan D, Dey A, Cook J, Harvey B, Menzies R, Macartney K. Surveillance of adverse events following immunisation in Australia annual report, 2013. *Commun Dis Intell Q Rep*. 2015;39(3):E369-86. http://www.ncbi.nlm.nih.gov/pubmed/26620351

91. Nemes E, et al. Optimization and interpretation of serial QuantiFERON testing to measure acquisition of M. tuberculosis infection. *Am J Respir Crit Care Med*. Vol 196 No 5, Sep 01, 2017. http://www.atsjournals.org/doi/pdf/10.1164/rccm.201704-0817OC

BELTA
Belgian Lung and Tuberculosis Association

FARES
Fonds des affections respiratoires asbl

VRGT