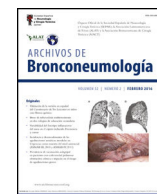




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SEPAR/ALAT Voice

Recommendations on the Diagnosis and Treatment of Tuberculosis Infection: SEPAR/SEIMC/Spanish Ministry of Health Consensus Statement[☆]

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ABSTRACT

All strategies on the pathway to tuberculosis (TB) elimination prioritise, among other measures, addressing tuberculosis infection (TBI), particularly the identification of individuals and population groups who should be candidates for tuberculosis preventive treatment (TPT).

In Spain, a TBI test is required before recommending TPT. An interferon-gamma release assay (IGRA) is preferred over the tuberculin skin test (TST), although the latter may be used in settings where IGRAs are not available or when deemed necessary to increase diagnostic sensitivity. On the other hand, new skin tests employing specific antigens (TBST) may play a key role.

Abbreviations: BCG, Bacillus Calmette-Guerin; CFP-10, 10 kDa culture filtrate protein; ESAT-6, 6 kDa early secreted antigenic target; H, isoniazid; HIV, human immunodeficiency virus; IFN- γ , interferon gamma; IGRA, interferon-gamma release assay; MDR-TB, multidrug resistant tuberculosis; P, rifapentine; PCR, polymerase chain reaction; R, rifampicin; SEIMC, Spanish Society for Infectious Diseases and Clinical Microbiology; SEPAR, Spanish Society of Respiratory Pathology; TB, tuberculosis; TBST, *M. tuberculosis* antigen-specific skin test; TBI, tuberculosis infection; TNF, tumour necrosis factor α ; TPT, tuberculosis preventive treatment; TST, tuberculin skin test; WHO, World Health Organization.

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Latent tuberculosis infection
Tuberculosis preventive treatment
(TPT)
Interferon-gamma release assay (IGRA)
Tuberculin skin test (TST)
Consensus

As a general principle, screening for TBI should include all individuals at high risk for progressing from TBI to TB, as described in this guideline, prioritising pulmonary TB contacts, people living with HIV, immunocompromised individuals and those in other situations associated with an elevated risk of developing TB.

Once TBI has been diagnosed in these high-risk groups, the algorithm set out in this guideline should be applied to rule out TB disease. Once TB has been excluded, TPT should be recommended. The preferred regimen is daily isoniazid (H) plus rifampicin (R) for 3 months (3HR). However, once rifapentine becomes available in Spain, both the 1-month daily (1HP) and the 3-month weekly (3HP) regimens combining H and rifapentine (P) may also be used. Finally, measures must be taken to ensure adherence to TPT and to monitor and manage potential drug-related adverse effects.

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Considerations concerning terminology

In recent years, great advances have been made in understanding the pathogenesis of TB and the complex interaction between this pathogen and the immune response. Infection by *Mycobacterium tuberculosis* complex is now recognised to be a continuous spectrum from exposure to the mycobacterium up to overt disease. Hence, numerous authors consider the traditional dichotomous terminology of latent infection versus active tuberculosis to be insufficient or inadequate [1,2].

Nonetheless, this classification has been used effectively for decades, because it is simple, practical, and easy to understand for patients and healthcare workers: an individual with a latent infection could be treated with just one drug and would not spread the disease to others, while an individual with a diagnosis of TB disease would require several drugs and could transmit the disease, even in the absence of signs and symptoms in the case of respiratory TB.

Currently, there is no consensus among researchers regarding the use of this terminology. Terms such as TBI, latent TB infection, infection by *M. tuberculosis* complex, incipient TB, subclinical TB, and asymptomatic TB overlap and may cause confusion among patients, clinicians, and even TB experts themselves [3–6]. Further, given the indirect diagnostic techniques currently used, these terms cannot distinguish between the persistence of the mycobacterium in a quiescent or low-activity state and the presence of an adaptive immunological response after exposure to *M. tuberculosis* complex antigens.

Acknowledging these limitations, in this document, we have adopted the terminology recommended by the World Health Organization (WHO) and other expert groups, which suggest using the term “TB infection (TBI)” rather than latent TB. TBI is defined as the presence of an acquired immune response detectable by currently available diagnostic techniques against *M. tuberculosis* antigens (although not exclusive to this species) with no signs or symptoms of the disease. Consequently, we use the term “tuberculosis preventive treatment (TPT)” instead of “treatment of latent TB” [7]. Accordingly, we have opted to use the terms TB disease or simply “TB”, instead of “active TB”.

The importance of addressing tuberculosis infection

Tuberculosis remains the leading infectious cause of death worldwide. According to the WHO, out of the 10.8 million new cases estimated in 2023, 1.25 million died [8]. Notably, TBI affects a quarter of the world’s population [9]. Recognising and diagnosing TBI, and providing treatment at this stage, is key to preventing progres-

sion to TB disease and contributing to disease control worldwide [10,11].

In 2014, the WHO launched the END TB strategy with the ambitious goals of reducing TB incidence by 90% and TB-related deaths by 95% by 2035, compared to 2015. In this strategy, tackling TBI is a key measure to achieve these goals. In Spain, notified TB cases have progressively decreased over recent decades to 10 per 100,000 [12], allowing the country to be considered low-incidence. Despite this, the burden of TBI remains substantial and therefore must be addressed. TPT in populations at risk of developing TB has proven to be both effective and cost-effective in reducing TB incidence [13,14].

However, TPT is not without adverse effects and may entail significant costs. It is therefore essential to carefully identify the population at the greatest risk of progression to TB, ensuring the benefits outweigh the potential adverse effects. Factors such as demographic change, increasing use of immunosuppressive therapies and social vulnerability have resulted in a rise in the number of individuals with TBI who develop TB disease. It should be emphasised that TPT is crucial not only from a medical and public health perspective, but also from one of social justice. For the first time, the 2024 WHO report included data on the economic impact of TB on households, indicating that half of those in which a member has TB face catastrophic costs. In this context, preventing progression from TBI to the disease is also a measure that may mitigate social and healthcare inequalities [8].

The introduction of diagnostic techniques such as IGRAs and new skin tests based on specific antigens, along with shorter and more effective TPT regimens, has led the Spanish Society of Pulmonology and Thoracic Surgery (SEPAR) and the Spanish Society of Infectious Diseases and Clinical Microbiology (SEIMC), within the framework of the agreement signed with the Spanish Ministry of Health’s Division for HIV, Sexually Transmitted Infections, Viral Hepatitis, and Tuberculosis Control, to consider it necessary to develop a joint statement updating the national consensus on the diagnosis and treatment of TBI from 2010 [15] and 2016 [16]. This document is intended for healthcare professionals caring for populations at risk of having TBI and at risk of progression to TB disease.

In this consensus statement, a multidisciplinary group of experts addresses the integrated and sustainable management of TBI in Spain, with the objective of adapting the guidelines of the END TB strategy, the commitments made at the 2023 United Nations High-Level Meeting on the Fight Against Tuberculosis and WHO recommendations to recent technological advances and national requirements.

Pathogenesis of tuberculosis. The continuum from exposure to infection and disease

The pathogenesis of TB is a complex process involving a dynamic interaction between the invading microorganism and the host immune system. This interaction determines the course of the infection, from an initial innate immune response to the containment or clearance of the infection by the adaptive immune response in later stages, or the progression of the infection to disease. Understanding these processes is essential for the development of strategies for the diagnosis, monitoring and treatment of *M. tuberculosis*.

Following exposure to *M. tuberculosis*, the bacilli are inhaled into the respiratory tract and cross the mucosal barriers. The presence of the microorganism in lung tissue triggers an innate immune response, mainly involving resident alveolar macrophages, dendritic cells and neutrophils [17,18]. This effector immune response may clear the bacilli, eliminating the invader without leaving an imprint on immunological memory, and therefore, with current diagnostic tools, such exposed individuals are indistinguishable from those who have not been exposed to *M. tuberculosis*.

When clearance does not occur, the mycobacteria migrate to the lymph nodes via immune system cells and replicate in macrophages. In the lymph nodes, antigen-presenting cells interact with naïve T cells, stimulating their differentiation into active phenotypes that migrate to the lung and initiate an adaptive immune response, mainly mediated by interferon gamma (IFN- γ). This leads to macrophage activation, the production of stimulating cytokines and the release of microbicidal factors that contribute to bacterial control.

Replication of *M. tuberculosis* may be inhibited by a balanced immune response that restricts bacterial replication in macrophages and traps extracellular bacteria in containment structures called granulomas. In humans, granulomas consist of a core region composed of infected macrophages, which have differentiated into multinucleated giant cells, epithelioid cells, foamy macrophages and neutrophils, surrounded by lymphocytes (CD4 and CD8 T cells and B cells) and fibroblasts that form a peripheral fibrotic capsule [19]. In TBI, bacilli persist in the central region in a state of low metabolic activity, whereas in TB disease, they replicate within the granuloma.

Various survival and immune evasion mechanisms have been described, such as the creation of a microenvironment that hinders immune cell activity and inhibits the fusion of the phagolysosome through, among other mechanisms, the release of proteins such as 6 kDa early secreted antigenic target (ESAT-6) and 10 kDa culture filtrate protein (CFP-10) [20,21].

Granulomas recruit macrophages that become infected and may subsequently migrate to other sites, potentially contributing to disease dissemination [22,23]. Failure to contain *M. tuberculosis* within the granuloma may allow the bacilli to escape, spread through the circulatory system and cause pulmonary or extrapulmonary TB.

Immune responses to TBI or TB vary depending on age, sex and immune status [24]. It should be emphasised that the immune response in TBI is not static. Certain factors may induce subclinical reactivation, in which bacilli remain in a state of low replication but are still capable of being activated in situations that compromise the immune system. These episodes of partial reactivation do not always result in disease with clinical manifestations, but could increase the bacterial burden and risk of transmission [25].

Thus, the simplified concept of individuals being classified as non-infected, with TBI or with TB disease has been replaced by a broader continuum of possibilities, where interactions between the environment, the host and the pathogen determine an individual's status at any given time. This paradigm shift, however, does not invalidate the diagnostic and treatment strategies for TBI in indi-

viduals at high risk of reactivation, given that they have shown to be effective in the control of TB in the community [17].

Current picture of tuberculosis infection and disease worldwide and in Spain

Worldwide, around 10.8 million people develop TB every year. In 2023, 1.25 million people died from TB, including 161,000 living with HIV [8]. In Spain, 4207 cases were reported in 2023, with an incidence 8.2 cases per 100,000 among autochthonous individuals ($n = 3944$), representing a 7% increase compared to 2022, but a 22.5% decline relative to 2015, when 4913 cases were reported (10.6/105). In 2023, 241 deaths were attributed to TB, a mortality of 0.5 per 100,000 (0.8 in men and 0.23 in women). Based on these data, Spain is considered a low-incidence country [12,26]. Nevertheless, further efforts are needed to develop a national plan for TB prevention and control [27].

Globally, the prevalence of TBI lies between 21.2% and 24.8%, corresponding to some 2 thousand million people infected [9,28]. There is a downward trend over the years, with rates decreasing from a WHO estimate in 1999 that a third of the world's population was infected to a mean of 23.7% reported in 2019 [29,30]. TBI prevalence is related to transmission rates and duration of the infection [31,32], and varies across continents, regions, age groups and other risk factors. By WHO region, the highest prevalence of TBI is found in Southeast Asia (30.8%), followed by the Western Pacific (27.7%), Africa (22.4%), the Eastern Mediterranean (16.3%), Europe (13.7%), and the Americas (11%) [9].

In Spain, the prevalence of TBI varies by regions. Among TB contact cases in Madrid, Galicia and Barcelona, the prevalence rates in 2022–23 were 20.8%, 27.2% and 23.4%, respectively [33–35]. In migrants from high-prevalence countries and in vulnerable situations, TBI rates vary depending on their origin and context, from 17.9% to 40% [36–38], similar to rates in their regions of origin. Notably, the highest rates of TBI are found among people deprived of liberty—about 50–54%—though prevalence varies by age, region, and length of incarceration. When IGRAs are used for diagnosis, lower rates (19–30.1%) are reported [39–41].

Healthcare workers are at increased risk of exposure, and the prevalence observed in this group ranges from 11.1% to 15.5%, depending on their origin and professional profile [42,43].

Among vulnerable populations at a high risk of progression to TB, the prevalence of TBI varies from 27.2% in nursing homes [44], to 2.6% in minors who visit their parents' high-TB-incidence country of origin [45]. In patients who are candidates for biological therapies, a prevalence of TBI of around 4.5% has been observed [46–48].

Diagnosis of tuberculosis infection

The diagnosis of TBI is indirect and based on the detection of a host immune response to *M. tuberculosis* complex antigens, without assessing the viability of the microorganism. The currently available diagnostic tests are described below, highlighting their strengths and limitations.

Interferon gamma release assays

These are in vitro blood tests that measure either the amount of IFN- γ released or the number of T cells releasing IFN- γ in response to specific antigens of *M. tuberculosis* complex (ESAT-6 and CFP-10). These antigens are absent from the *Mycobacterium bovis* BCG vaccine and most non-tuberculous mycobacteria, except for *Mycobacterium marinum*, *Mycobacterium kansasii*, *Mycobacterium szulgai* and *Mycobacterium flavescens*. Several commercial kits are available [49] (Table 1), the most widely studied being:

Table 1
IGRA techniques used for the diagnosis of tuberculosis infection.

Technique	T-SPOT.TB	QFT-plus	LIAISON QFTplus	AdvanSure™ TB-IGRA	Wantai TB-IGRA	Standard E TB-feron	QIArearch QFT	ichroma™ IGRA-TB	VIDAS™ TB-IGRA	T-Track® TB
Manufacturer	Oxford, Immuntotec, UK	Hilden, Germany	DiaSorin S.P.A., Italy	LG Life sciences, South Korea	Wantai, China	SD Biosensor, South Korea	Hilden, Germany	Boditech Med Inc., South Korea	bioMérieux SA, Marcy-l'Etoile, France	Mikrogen GmbH, Neuried, Germany
Sample Type of antigen	PBMC Panel A: ESAT-6 Panel B: CFP-10	Whole blood ESAT-6, CFP-10	Whole blood ESAT-6, CFP-10	Whole blood ESAT-6, CFP-10	Whole blood ESAT-6, CFP-10	Whole blood ESAT-6, CFP-10, and TB7.7 recombinant proteins	Whole blood Peptide cocktail simulating ESAT-6 and CFP-10	Whole blood ESAT-6, CFP-10	Whole blood ESAT-6, CFP-10	Whole blood ESAT-6, CFP-10
Tubes	1 tube	Nil, TB1, TB2, and mitogen tubes	PC, TB-A, TB-B, and negative control	Nil, TB1, TB2, and mitogen tubes	Nil, TB1, TB2, and mitogen tubes	Nil, TB1, TB2, and mitogen tubes	Blood collection tube and processing tube	Nil, TB1, TB2, and mitogen tubes	Nil, TB1, TB2, and mitogen tubes	Nil, TB1, B2, and mitogen tubes
Technology platform	ELISPOT	ELISA	CLIA	CLIA	ELISA	ELISA	LFIA	FIA	ELISA	RT-qPCR
Results	Number of cells that release IFN-γ	Amount of IFN-γ released by CD4/CD8 T cells	Amount of IFN-γ released by CD4/CD8 T cells	Amount of IFN-γ released by CD4/CD8 T cells	Amount of IFN-γ released by CD4/CD8 T cells	Amount of IFN-γ released by CD4/CD8 T cells	Amount of IFN-γ released by CD4/CD8 T cells	Amount of IFN-γ released by CD4/CD8 T cells	Amount of IFN-γ released by CD4/CD8 T cells	Changes in IFNG and CXCL10 mRNA levels
Sensitivity	83%	91.4%	78.6%	98.48%	86.4%	88%	96.5%	95.76%	97.5%	94.9%
Specificity	83%	97.8%	94.7%	97.95%	85.9%	95%	94.2%	88%	97.6%	93.8%

Adapted from Li LS, Yang L, Zhuang L, Ye ZY, Zhao WG, Gong WP. From immunology to artificial intelligence: revolutionizing latent tuberculosis infection diagnosis with machine learning. *Mil Med Res*. 2023 Nov 28;10 [1]:58. doi:10.1186/s40779-023-00490-8.

PBMC: peripheral blood mononuclear cells; ELISPOT: enzyme-linked immunosorbent spot; ELISA: enzyme-linked immunosorbent assay; CLIA: chemiluminescent immunoassay; IFN-γ: interferon gamma; LFIA: lateral flow immunoassay; FIA: fluorescence immunoassay; T.SPOT: T cell spot test; QFT-Plus: QuantiFERON-TB Gold-In-Tube; IGRA: Interferon gamma release assay, QIArearch: Qiagen kit for detecting *M. tuberculosis*; VIDAS: registered trademark of bioMérieux; ESAT-6; 6 kDa early secreted antigenic target; CFP-10: 10 kDa culture filtrate antigen, coded by the *esxB* gene and secreted to the medium; Nil: Null or negative control; PC: positive control; TB-A: tuberculosis A; TB-B tuberculosis-B; NC: negative control; RT-qPCR, reverse transcription quantitative polymerase chain reaction; IFN-G: interferon gamma gene; CXCL: chemokine (C-X-C motif) ligand.

- a) QuantiFERON-TB Gold Plus (QFT-Plus) [50–52]. This test is based on four tubes, two of which contain specific polypeptide antigens (CFP-10 and ESAT-6) that stimulate CD4+ and CD8+ T cells, potentially relevant for identifying recent infections or active infectious states. The response is measured using ELISA or chemiluminescence immunoassays [53].
- b) T-SPOT.TB [54]. This test quantifies IFN- γ -producing T cells, and readings are based on ELISPOT assays.

Results are interpreted as positive, negative or indeterminate, based on the response to stimulation with specific antigens, taking into account the internal positive and negative controls.

Indeterminate results are uncommon and can be due to: (1) pre-analytical or analytical errors, or failure of the positive and/or negative controls, and (2) patient-related factors: viral infections that impair cellular immunity (e.g. HIV with low CD4 T cell counts), immunosuppressive medications (corticosteroids, chemotherapy, biologics), autoimmune and/or haematological malignant disease, chronic conditions (diabetes, chronic kidney failure, advanced liver disease) or extreme age.

The main strength of IGRAs is their high specificity, as results are not affected by prior BCG vaccination, and only a few non-tuberculous mycobacterial species interfere with the results. Moreover, IGRAs have been shown to be more sensitive than TSTs in immunosuppression, slightly more so with the ELISPOT assay [55], they require only a single patient visit, and provide objective results.

Their main limitations relate to their higher cost, the need for blood sampling and the requirements for laboratory facilities and specific technical training. In young children, their use is limited due to the weaker supporting evidence and higher rates of indeterminate results. As with TSTs, the sensitivity may be lower in immunosuppressed individuals, and the results cannot distinguish between TBI and TB [56–58].

Tuberculin skin test

The TST is the oldest diagnostic test currently recommended. It measures the delayed-type hypersensitivity response mediated by T cells, through an intradermal injection of a purified protein derivative (PPD) of *M. tuberculosis* into the upper third of the flexor surface of the forearm (Mantoux method) [59].

For interpretation, the diameter of the induration (skin thickening) should be measured rather than the erythema. Although different cut-off points have been accepted depending on individual and epidemiological risk factors for developing the disease [60], the test should be performed in people for whom a positive result would prompt preventive treatment. In this context, an induration of ≥ 5 mm would be the main outcome used as a cut-off for recommending TPT. Higher cut-offs (≥ 10 or ≥ 15 mm) may be appropriate in epidemiological studies or in individual cases where the efficacy of TPT has not been sufficiently demonstrated.

The main strengths of the TST are its low cost, wide availability, and performance at the point of care, without the need for laboratory facilities. In addition, the test is supported by almost a century of evidence of its utility, particularly in children.

Its limitations are related to the lack of specificity, with positive reactions occurring due to prior BCG vaccination or exposure to non-tuberculous mycobacteria. Further, it has variable sensitivity, which is influenced by immunosuppression. The test has no internal positive and/or negative controls. Operationally, it requires two patient visits (one for the injection, and another 48–72 h later, for reading the response), and the results are more subjective and less reproducible than those of IGRAs.

Skin tests with specific antigens of *M. tuberculosis* complex (TBST)

In recent years, skin tests have been developed and marketed that, unlike the TST, only contain highly specific antigens of the *M. tuberculosis* complex. Consequently, their specificity is higher than that of the TST [61–64]. They are also performed using the Mantoux method, with the transverse diameter of the induration measured after 48–72 h. The results are interpreted according to the same criteria as the TST [65].

Various commercial tests are available including:

- a) Cy-Tb (SIILTIBCY®) formerly known as the C-Tb test. It contains two recombinant proteins, ESAT-6 and CFP-10. It is the only test currently approved and marketed in Spain.
- b) Diaskintest®. It is based on a recombinant protein produced using a genetically modified culture of *Escherichia coli* BL21 (DE3)/pCFP-ESAT.
- c) C-TST. The active ingredient is a recombinant fusion protein ESAT-6–CFP-10, expressed in genetically modified *E. coli*.

Recent innovations in the diagnosis of tuberculous infection

Alongside numerous improvements in established testing kits, rapid or ultra-rapid IGRAs are being developed, using miniaturised microfluidic systems and flow cytometry-based platforms to achieve same-day results (within 24 h). In addition, researchers are exploring immunological biomarkers and molecular and transcriptomic tests, with higher positive predictive values for disease progression, but these are not yet available for clinical use [49,55,66–68]. The ultimate goal is to develop a test that not only diagnoses TBI but also identifies individuals at highest risk of progression to TB disease, thereby enabling more targeted and efficient TPT.

Current diagnostic algorithms

The diagnosis of TBI requires integrating microbiological, clinical and epidemiological factors. In high-prevalence regions, which are often those with fewer economic resources, WHO recommends prioritising TSTs as the initial screening tool, with subsequent confirmation by IGRA (for example, in individuals previously vaccinated with BCG) [65,69,70].

In low-prevalence regions, which typically have greater economic and social resources – such as Spain, the recommendation is to perform an IGRA, particularly in people who have received the BCG vaccine. In certain circumstances, a combination of TST and IGRA may be considered, or even the simultaneous use of two different IGRA techniques, to enhance diagnostic sensitivity [65,71–73].

Recent evidence indicates that a negative IGRA or TST result has an almost 100% negative predictive value for the development of disease. This requires that testing is technically well performed, before the initiation of any immunosuppressive or immunomodulatory treatment, and in the case of contacts, at least 8–12 weeks after exposure (window period) [56,70,74–78].

Several studies have also demonstrated the superiority of IGRAs over TSTs in predicting the development of the disease [69,74,79–81].

In children <5 years of age (and especially in those <2 years of age), TST (or TBST) plus IGRA is recommended to achieve maximum diagnostic sensitivity. In immunocompetent individuals >5 years of age, either TST (or TBST) or IGRA may be used. IGRAs or TBSTs, are particularly recommended for children who have received BCG vaccination [82].

Pending further data on the role of new antigen-specific skin tests, this guideline supports the use of IGRAs as the initial diagnostic test, reserving TSTs for settings with limited access to IGRAs

Table 2
Risk of developing tuberculosis among individuals infected with *M. tuberculosis*.

Risk factor	Relative risk compared to the general population
High risk (tuberculosis infection tracing)	
HIV	10–100
Solid organ or blood transplant	20–70
Close contacts	15
Silicosis	2.8
Chronic kidney failure requiring dialysis	6.9–52.5
Apical fibronodular changes on X-ray	6–19
Treatment with TNF inhibitors	1.6–25.1
Moderate risk	
Treatment with corticosteroids	2.8–7.7
Diabetes mellitus	1.6–7.83
Immigrant from high-TB-prevalence countries	2.9–5.3
Treatment with biologics: ^a	
IL-6R inhibitors (tocilizumab, sarilumab)	
JAK inhibitors (baricitinib, upadacitinib, tofacitinib)	
Low risk	
Body mass index ≤ 20 kg/m ²	2–3
Smoker (20 cigarettes/day)	2–3.4
Lung granuloma on chest X-ray	2
Treatment with biologics: ^a	
CTLA4lg (abatacept), IL-12/23 inhibitor (ustekinumab), IL-23 inhibitors	
(guselkumab, risankizumab), IL-17 inhibitors (secukinumab, ixekizumab)	

Adapted from Ai JW, Ruan QL, Liu QH, Zhang WH. Updates on the risk factors for latent tuberculosis reactivation and their managements. *Emerg Microbes Infect.* 2016 Feb 3;5 [2]: e10.

^a Picchianti-Diamanti A, Aiello A, De Lorenzo C, Migliori GB, Goletti D. Management of tuberculosis risk, screening and preventive therapy in patients with chronic autoimmune arthritis undergoing biotechnological and targeted immunosuppressive agents. *Front Immunol.* 2025 Feb 3;16:1494283.

or operational constraints, such as large-scale community contact tracing studies (e.g. schools, universities, or workplaces). In situations where higher diagnostic sensitivity is needed, both tests may be performed.

In any case, it should be noted that no TBI diagnostic technique, whether alone or in combination, can guarantee with absolute certainty the prevention of tuberculosis disease [83]

Tuberculosis preventive treatment

Identification of populations requiring preventive treatment

It is estimated that 5–15% of individuals infected with *M. tuberculosis* complex will develop TB disease during their lifetime. Therefore, when selecting populations to receive TPT, emphasis should be placed on those groups at the highest risk of progression to disease. This requires consideration of the context in which testing is performed and the strategy applied, whether through contact tracing or population screening.

In the context of a TB control programme, it is essential to consider the number of infected individuals who must be treated to prevent one case of disease, together with the efficacy of, and adherence to, preventive treatment. In short, the aim is to maximise the efficiency of this intervention. Accordingly, the highest-priority group for evaluation is contacts of patients with pulmonary TB, in whom the risk of progression to disease is markedly increased, particularly among household and close contacts. This risk varies as a function of age, being highest in children under 5 years, although in older individuals it may reach up to 28% [84–86]. Therefore, all contacts of a pulmonary TB case should be prioritised for TPT, irrespective of age, especially if they have shared living space for more than 3–6 h a day.

In contacts at high risk of rapid progression to TB disease (children under 5 years or individuals with severe immunosuppression), initiation of TPT should be considered even in the presence of a negative IGRA or TST result. In individuals exposed to patients with pulmonary TB who initially test negative by TST or IGRA, testing should be repeated 8–12 weeks after the latest exposure; TPT is

indicated if the result subsequently becomes positive [77,87,88]. Reverse contact tracing (to identify the source of infection) should be performed in cases of childhood TB, including extrapulmonary forms [27].

In clinical practice, the risk of TB development must be balanced against the potential toxicity of TPT. Table 2 summarises the risk factors for developing TB in infected individuals, classified as high, intermediate, or low risk [89]. In this context, screening for TBI should be performed in individuals at high-risk, prioritising people living with HIV, as well as the following groups: patients starting treatment with TNF inhibitors, those with end-stage renal disease, solid-organ or haematological transplant recipients, and individuals with silicosis, where the benefit of TPT clearly outweighs the associated risks [7,90,91]. It has also been suggested that the presence of fibrotic pulmonary lesions ≥ 2 cm² in infected individuals with no previous TB treatment should be an indication for TPT [92–95]. TBI testing may also be considered on a case-by-case basis in individuals receiving biological agents such as IL-6R or JAK inhibitors, where the risk of developing TB disease is not negligible [96,97].

In other scenarios, such as patients with diabetes, gastrectomy, alcohol misuse, solid-organ or haematological malignancies, or long-term corticosteroid therapy, the benefits of TPT are less certain; therefore, TBI screening and treatment should be considered on an individual basis [98,99]. In individuals diagnosed with TBI during contact tracing of a patient with pulmonary TB who decline TPT, clinical and radiological follow-up should be undertaken every 6–12 months for two years (the period of highest risk of progression to TB disease after infection). [100,101]

In frontline healthcare workers, people deprived of liberty, migrants from high TB-prevalence countries (particularly minors and those who have arrived within the past five years), people experiencing homelessness and individuals with substance use disorders may also be considered for TPT on a case-by-case basis [7,38,102]. The decision to recommend TPT in patients previously treated for TB or TBI should likewise be individualised. In such situations, TBI tests are usually positive and cannot distinguish whether reinfection has occurred. It should also be noted that individuals

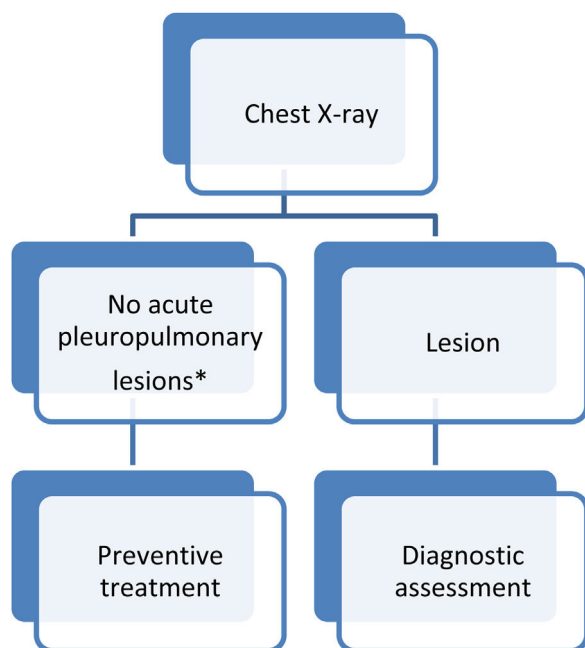


Fig. 1. Algorithm to rule out tuberculosis in asymptomatic individuals. * Consider diagnostic evaluation in patients with severe immunosuppression, or if C-reactive protein > 5 mg/L in patients living with human immunodeficiency virus.

with a prior episode of TB are at increased risk of developing disease again if reinfected with *M. tuberculosis* [103,104].

Algorithm to rule out tuberculosis disease

Before starting preventive treatment, it is essential to rule out TB disease.

In immunocompetent individuals without symptoms suggestive of TB (cough, haemoptysis, fever/low-grade fever, weight loss, night sweats), chest radiography has a sensitivity exceeding 90–95%; therefore, the absence of lesions can be reasonably used to rule out pulmonary TB [105].

In people living with HIV, symptoms have a sensitivity of 83%, but low specificity (38%), which is not improved by radiology (20%). However, when combined with C-reactive protein levels > 5 mg/L, specificity increases to 76%, and to 90% in outpatients on antiretroviral therapy [105,106].

Fig. 1 shows an algorithm for ruling out TB disease in infected individuals. It highlights the performance of a chest X-ray to exclude TB. Rapid molecular techniques (real-time PCR and others) should be considered in individuals with symptoms and/or radiological findings suggestive of TB [27].

Preventive treatment options for tuberculosis infection

The first evidence suggesting that TPT could be effective was published more than 50 years ago, demonstrating the efficacy of long-term H monotherapy [92,107–117]. At that time, H was the only drug with both strong activity and good tolerability against the *M. tuberculosis* complex, and all studies conducted over the following three to four decades were based on H. Numerous clinical trials and publications consistently showed its efficacy when administered for six to nine months.

Although maximum efficacy was achieved with 9–10-month regimens provided adherence was good [118,119], field studies demonstrated that 6 months was similarly effective, as longer

regimens of 9–12 months were associated with higher treatment discontinuation rates [92,118,119]. Based on this evidence and some subsequently published meta-analyses [120], the tendency for decades has been to recommend a 6-month regimen with H [121–125].

Nonetheless, it has been known for decades that the main activity of H lies in its bactericidal properties [126–128], acting mainly against continuously replicating bacilli, while it has limited sterilising effect against bacilli in a latent or semi-latent state. Given this, H cannot be considered the best drug for TPT, since its efficacy depends on prolonged administration over many months (to allow the bacilli in a latent/semi-latent state to replicate).

An ideal TPT drug should have sterilising activity, since this allows treatment durations to be shortened [126–128]. In recent years, numerous randomised clinical trials have evaluated such drugs, mainly rifamycins, particularly P and R [113,115,120,129–139]. These studies have demonstrated that the efficacy of 3-month daily R combined with H (3HR) [113,115,129–132], 4-month daily R [113,120,133,134], 3-month weekly HP [135–138] and 1-month daily HP [139,140] is similar to 6–9 months of H monotherapy, with the major advantage of shortening treatment duration, which improves adherence. However, these regimens may be associated with drug-drug interactions, as rifamycins are potent inducers of cytochrome P450.

Table 3 lists the TPT regimens that have been shown to be effective and safe, together with the recommended doses by age group, with some comments on their indication [7,113,115,120,129–139].

Based on its shorter duration, the 1HP regimen (daily dosing) would be the preferred option, particularly for people living with HIV. At present, however, it is not recommended for individuals under 14 years of age, as this age group has not been included in clinical trials, and therefore no scientific evidence is available, although it is reasonable to assume that it may also be effective [7,139,141,142]. The second option for TPT would be the 3HP regimen (weekly dosing), which requires only 12 doses in total, a feature that may facilitate adherence and supervised administration when deemed necessary. Although the WHO advises against the use of P during pregnancy due to the lack of evidence regarding its non-teratogenicity [7], some studies have reported a safety profile comparable to that of other TPT regimens [143], and its use in pregnant women may therefore be considered [144]. At the time of writing this report, P is not available in Spain or many other European countries, making the recommendation of 1HP or 3HP regimens unfeasible. Accordingly, the regimen of choice in Spain remains 3HR, with 6–9H reserved as an alternative in cases where R cannot be used due to toxicity, drug interactions, or mono-resistance to R. A study in Spain found the 3HR regimen to be the most cost-effective [145].

In individuals who have been in contact with TB patients with mono- or polyresistance to H, or intolerance to it, the treatment of choice for TPT is 4R [7,113,120,133,134]. In contacts of patients with multidrug-resistant TB (MDR-TB, resistant to at least H and R), 6 months of levofloxacin is recommended [7,146–148]. In this regard, there is no evidence for the efficacy of any TPT for contacts of patients with pre-extensively drug-resistant TB (MDR-TB that is also resistant to at least fluoroquinolones), and therefore these individuals should be managed on a case-by-case basis. Delamanid may be a good option given its mechanism of action [128].

The effectiveness of TPT in preventing TB disease is directly related to adherence. It is therefore essential to encourage each patient to fully adhere to the prescribed treatment throughout the diagnosis and treatment processes, especially among vulnerable populations [149]. Specialised TB units have achieved high rates of TPT adherence [150–153].

Table 3

TPT regimens shown to be effective. Doses and observations.

Regimen	Doses	Observations
1 HP	H: 300 mg/day P: 600 mg/day Fixed dose (regardless of body weight)	Not currently recommended for individuals <14 years old Check for drug interactions ^a
3 HP, weekly	H: 900 mg/dose P: 900 mg/dose	12 doses in total. Check for drug interactions ^a
3 HR	H: - >10 years old: 5 mg/kg/day - <10 years old: 10 mg/kg/day (range, 7–15 mg) Maximum dose: 300 mg/day R: - >10 years old: 10 mg/kg/day - <10 years old: 15 mg/kg/day (range, 10–20 mg) Maximum dose: 600 mg/day	Check for drug interactions ^a
R	R: - >10 years old: 10 mg/kg/day - <10 years old: 15 mg/kg/day (range, 10–20 mg) Maximum dose: 600 mg/day	Check for drug interactions ^a
6–9 H	H: - >10 years old: 5 mg/kg/day - <10 years old: 10 mg/kg/day (range, 7–15 mg) Maximum dose: 300 mg/day	
6 Lfx	Levofloxacin: - >14 years old, based on body weight: - <50 kg, 500 mg/day; - ≥50 kg, 750 mg/day - ≤15 years old (range, approx. 15–20 mg/kg/day): - 6–10 kg: 150 mg/day; - 10–15 kg: 200 mg/day - 15–25 kg: 250–300 mg/day - 25–45 kg: 500 mg/day	Although there are no comparative data, moxifloxacin can be used if levofloxacin cannot be used.

^a Rifamycins (rifampicin –R– and rifapentine –P–) are potent inducers of some enzymes of cytochrome P450, and accelerate the metabolism of some drugs, reducing their effect. These include some antiretrovirals, antiepileptics, antiarrhythmics, quinines, oral anticoagulants, antifungals, medical contraceptives, corticosteroids, ciclosporin, mycophenolate, quinolones, and other antimicrobials, antihyperglycemic agents, methadone and tricyclic antidepressants.

Preventive treatment-related adverse reactions and drug interactions

As with any other drug, TPT entails the risk of adverse effects, which may be serious; therefore, patients should be monitored through clinical follow-up and laboratory testing as deemed appropriate.

Serious adverse effects are uncommon, appearing in fewer than 5% of cases in most series [7,154,155], the most frequent being liver toxicity and dyspepsia. Factors such as older age, alcohol misuse, baseline liver disease, immunosuppressive medication, and malnutrition may increase the risk of toxicity [156–160]. The 6–9-month regimens with H are associated with slightly higher rates of hepatotoxicity than shorter treatments with R, P or H and R [134,135,139,161–163]. On the other hand, H and P containing regimens are associated with higher rates of cutaneous, flu-like or systemic adverse effects that may occasionally require discontinuation of treatment [161,164–166].

Although some researchers do not recommend systematic blood testing before TPT in patients at low risk of developing toxicity [7], in our setting, we recommend baseline laboratory testing, as well as monitoring during treatment, including at least liver function tests. Patients should be advised that in the event of signs of liver toxicity, they must contact a healthcare professional, who will assess the need for additional blood tests (including liver function tests). Warning signs and symptoms include severe dyspepsia, vomiting, fever, and jaundice of the skin or mucous membranes. Fig. 2 presents an action plan for suspected toxicity and/or the presence of compatible symptoms. In healthy children, adverse drug effects are rare; therefore, only a baseline test is recommended, with repeat testing indicated only if signs or symptoms suggestive of toxicity appear.

Other relatively common adverse effects are listed in Table 4.

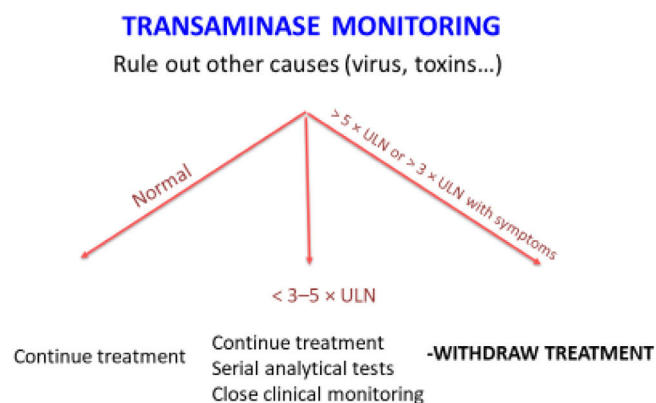


Fig. 2. Algorithm for the management of suspected hepatotoxicity due to antituberculosis drugs. ULN: upper limit of normal value.

As a general rule, any medication associated with a previous serious adverse effect in a given patient should not be reintroduced; instead, an alternative treatment should be considered [7,167,168].

Conclusions

As stated in these recommendations, a comprehensive approach to TBI is a key strategy in the pathway towards TB elimination.

In Spain, testing for TBI should be performed before indicating TPT, with IGRA preferred over TST, although newer antigen-specific skin tests may play a relevant role in the near future. All individuals at high risk of developing TB should undergo diagnostic TBI testing as described in this document. Once TBI has been diagnosed and TB excluded, TPT should be initiated. At present, the preferred regimen is 3HR, although 1HP and weekly 3HP are expected to become

Table 4
Adverse effects of drugs used in tuberculosis preventive treatment.

Drug	Common	Uncommon
Isoniazid	Elevated liver enzymes in asymptomatic patients Hepatitis Peripheral neuropathy Skin rash	Seizures Joint pain Lupus-like syndrome Acne
Rifampicin	Sleepiness, lethargy Dyspepsia Elevated liver enzymes in asymptomatic patients Hepatitis Skin rash Thrombocytopenia	Psychological disturbances Pancreatitis Acute kidney failure Haemolytic anaemia Flu-like signs and symptoms Hypoprothrombinaemia
Rifapentine	Discolouration of urine and/or other bodily fluids Dyspepsia Flu-like signs and symptoms Skin rash Hepatitis	Low blood pressure Leucopenia Anaemia Anorexia
Levofloxacin	Discolouration of urine and/or other bodily fluids Diarrhoea Dyspepsia Nausea, vomiting Joint pain	Hypoprothrombinaemia Tendinopathy Hepatitis Muscle pain Peripheral neuropathy Insomnia Prolonged QTc interval Altered taste and smell

Ref: Adapted from WHO operational handbook on tuberculosis. Module 1: prevention – tuberculosis preventive treatment, second edition. Geneva: World Health Organization; 2024 (<https://iris.who.int/handle/10665/378535>).

options once rifapentine becomes available in our setting. Ensuring and promoting adherence to TPT is essential.

In addition to the correct and early diagnosis and treatment of TB and TBI, effective control of the disease requires thorough and appropriate management of cases, their contacts, and groups at high risk of developing TB disease. For this purpose, it is essential to notify all cases, ensure accurate contact tracing, and implement appropriate screening actions for both TB and TBI, within a multidisciplinary approach under the framework of a TB control programme.

Ethical statement

This work is part of the Agreement between the Directorate General of Public Health and Health Equity of the Ministry of Health, the Spanish Society of Pulmonology and Thoracic Surgery, and the Spanish Society of Infectious Diseases and Clinical Microbiology, for the development of activities within the framework of addressing tuberculosis (Resolution of November 25, 2024; Official State Gazette, December 21, 2024).

Declaration of generative AI and AI-assisted technologies in the manuscript preparation process

During the preparation of this work, the authors used ChatGPT in order to improve readability and language, and NapkinAI to enhance the Visual Abstract. After using these tools, the authors reviewed and edited the content as needed and take full responsibility for the content of the published article.

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Conflicts of interest

The authors declare that they have no conflicts of interest that could be considered to influence, directly or indirectly, the content of the manuscript.

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