

# Pulmonary tuberculosis

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## Abstract

*Tuberculosis disease (TB) is the leading cause of death by a single infectious agent in the world and contributes significantly to infant mortality. Pediatric TB has been a hidden epidemic due to its low infective capacity and lower incidence compared to adults. Currently the greatest limitations are the difficulties in diagnosis and the absence of optimal pediatric formulations. Although pediatric TB mortality is exceptional in our setting, there is a significant morbidity caused especially by extrapulmonary forms of the disease. Furthermore, although Spain is considered a low-incidence country, it is the Western European country with the highest number of cases. The role of the Primary Care pediatrician is essential in the initial management of these patients and their families, as well as in the ongoing follow-up and support throughout the course of the disease.*

**Key words:** Pediatric tuberculosis; Exposure; Latent tuberculosis infection; Tuberculosis disease; Tuberculosis treatment.

**Palabras clave:** Tuberculosis pediátrica; Exposición; Infección tuberculosa latente; Enfermedad tuberculosa; Tratamiento de tuberculosis.

## Resumen

La tuberculosis (TB) es la principal causa de muerte por un solo agente infeccioso en el mundo y contribuye de forma notable a la mortalidad infantil. Sin embargo, la TB pediátrica ha sido una epidemia oculta por su escasa capacidad infectiva y menor incidencia comparada con adultos. Actualmente, las mayores limitaciones son las dificultades en el diagnóstico y la ausencia de formulaciones pediátricas óptimas. A pesar de que en nuestro medio la mortalidad por TB pediátrica es excepcional, existe una importante morbilidad ocasionada especialmente por las formas extrapulmonares. Además, aunque España es considerada un país de baja incidencia, es el país de Europa occidental con el mayor número de casos. El papel del pediatra de Atención Primaria es fundamental en el abordaje inicial de estos pacientes y de las familias, así como en el seguimiento y acompañamiento de la enfermedad.

## Introduction

Tuberculosis is an infection caused by *Mycobacterium tuberculosis*, transmitted via the respiratory route from bacilliferous adults. Children rarely transmit the disease, and it is often not microbiologically confirmed. In pediatrics, its diagnosis is a “sentinel event”, indicating recent transmission. Children from or exposed to environments with high endemicity, as well as younger children and immunocompromised individuals, are at greater risk of acquiring tuberculosis and developing severe forms of the disease.

Tuberculosis (TB) is an infectious disease caused by *Mycobacterium tuberculosis* (MTB), an acid-fast bacillus (AFB). The infection is transmitted through the respiratory route, by inhaling contaminated droplets from infected individuals (positive sputum smear microscopy). Children are not usually transmitters due to their lower bacterial load in respiratory secretions, which, combined with their in-

ability to expectorate, means that microbiological confirmation is not achieved in up to half of cases<sup>(1)</sup>. The diagnosis of infection or disease in a child is always a “sentinel event” that reflects recent MTB transmission in the community; even if it is not proven, there is always a nearby adult with tuberculous bacillary disease. All children in contact with MTB should be properly diagnosed with exposure, infection, or disease.

## OBJECTIVES

- To present the clinical forms and diagnostic methods of pediatric tuberculosis.
- To identify the risk factors for acquiring an infection or tuberculosis disease.
- To learn how to perform a proper medical history and targeted physical examination.
- To perform appropriate diagnostic guidance in the initial screening.
- To select cases that require follow-up in a specialized unit.

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The development of one or the other status will depend on the closeness of contact with the TB-positive bacillary source, the number of bacilli in the source, the duration of exposure, the child's immune status, and age.

Children who are immigrants from highly endemic regions or who live with immigrant adults from these regions, as well as travelers to endemic areas, are at greater risk of acquiring the infection. Children, especially young children, and immunocompromised patients are at greater risk of progression from tuberculosis infection to disease and of developing severe disease<sup>(2)</sup>.

## Epidemiology

**Tuberculosis is a global emergency that causes 1.3 million deaths annually, making it the leading cause of infectious mortality in childhood, with a particularly severe impact on children under five. Multidrug-resistant strains are of particular concern, and although the incidence in Spain is decreasing, it remains the highest in Western Europe, justifying systematic screening of immigrant children from high-endemic areas.**

Tuberculosis (TB) is considered a global health emergency by the WHO, with 1.3 million deaths annually, primarily in low-income countries. It is the leading cause of death from a single infectious agent in childhood, especially in children under 5 years old. For every child with TB disease, it is estimated that there are 10 latently infected children who, having not yet developed the disease, are the future TB reservoir. In general, pediatric TB affects infants and adolescents and is less common between the ages of 5 and 10. Currently, there is great concern about the increase in cases of multidrug-resistant TB (MDR-TB), particularly in Eastern European countries, where it accounts for 16% of new diagnoses. The incidence of MDR-TB in children is not well understood, but it is thought to be similar to that in the adult population. Through the "End TB" strategy, the WHO aims to reduce TB incidence by 80% and TB mortality by 90% by 2035<sup>(3)</sup>.

Spain has the highest number of pediatric cases in Western Europe, although the incidence is gradually

decreasing<sup>(4)</sup>. In the pediatric population of our country, the incidence of the disease is 3 cases/100,000 children<sup>(5)</sup>.

The factors that determine endemicity in developed countries are primarily the prevalence of human immunodeficiency virus (HIV) infection and the percentage of immigrants from countries with a high prevalence of TB. In recent decades, immigration has increased, sometimes originating from areas with higher rates of drug resistance. In our region, the percentage of MDR-TB in the general population is around 4% and is higher in the immigrant population<sup>(6)</sup>. For all these reasons, TB screening is recommended for all immigrant children from areas of high endemicity, in order to detect infection early, identify sources of transmission, and interrupt the transmission cycle.

## Pathophysiology

**Childhood pulmonary tuberculosis begins after the inhalation of *Mycobacterium tuberculosis*, which settles in the alveoli and forms the primary Ghon complex. In most immunocompetent children, the cellular response contains the infection in a latent form. In infants and young children, immune immaturity favors hematogenous dissemination and the development of severe forms, such as miliary tuberculosis or tuberculous meningitis.**

Childhood pulmonary tuberculosis occurs after inhaling aerosols containing *Mycobacterium tuberculosis*, expelled by an adult with bacillary tuberculosis. Once in the lungs, the bacilli reach the alveoli and are phagocytosed by macrophages, where they can survive and replicate thanks to their immune evasion mechanisms. In the following days, the primary Ghon complex forms, consisting of the initial lung lesion and involvement of the regional lymph nodes. In most children, especially immunocompetent ones, the T-cell-mediated immune response manages to contain the infection in a latent form, although without achieving complete eradication.

In infants and young children, whose cell-mediated immunity is immature, containment of the bacillus is less effective, facilitating early dis-

semination from the pulmonary focus to the bloodstream and other organs. This vulnerability explains the higher frequency of severe forms in this group, such as miliary tuberculosis and tuberculous meningitis. In older children, progression to active pulmonary disease usually depends on factors such as the bacterial load of the index case, the intensity and duration of exposure, nutritional status, and the presence of comorbidities or immunosuppression.

## Definition of disease stages

### Exposure to tuberculosis

We consider exposure when: 1) there is recent (last 3 months) and close contact (>4 hours daily in the same enclosed space) with a confirmed/suspected patient of bacilliferous TB; 2) tuberculin skin test (TST) and/or IGRA (Interferon Gamma Release Assays) negative; and 3) absence of clinical symptoms and normal chest x-ray.

### Tuberculous infection (TBI)

We consider TBI to be present when: 1) the TST/IGRA test is positive; 2) there are no clinical symptoms and the chest X-ray is normal, regardless of whether there is known contact. In the absence of contact and without risk factors, a history of Bacillus Calmette-Guérin (BCG) vaccination with a positive TST and negative IGRA test is interpreted as an effect of the BCG, and these cases are not considered TBI.

### Tuberculosis disease

We consider TB disease to be present when at least two of the following are present: 1) compatible clinical presentation; 2) compatible radiological findings; 3) recent exposure or immunological evidence of contact (positive TST/IGRA); 4) adequate response to antituberculosis treatment<sup>(7)</sup>. A definitive diagnosis is provided by a culture or PCR positive for MTB, although, frequently in children, we do not obtain microbiological confirmation (paucibacillary forms), and a presumptive diagnosis is usually made. Immunological tests (TST/IGRA) are usually positive, although in early or disseminated forms they may be negative. In cases of clinical suspicion, despite a negative

immunological test, treatment should be initiated.

## Clinical presentation

**Symptoms are nonspecific and should raise suspicion of the disease when fever, prolonged cough, or constitutional symptoms are present in children exposed to TB cases or from areas of high endemicity. Although the disease can be multisystemic, the most frequent form is pulmonary, with lymph node involvement. Respiratory symptoms are usually insidious and may be accompanied by constitutional manifestations or signs of severity, although many children in low-prevalence countries remain asymptomatic or have very mild symptoms.**

The symptoms of the disease are nonspecific. We should suspect it when there are subtle symptoms such as constitutional symptoms, fever, or a prolonged cough, in people living with chronic coughs or those diagnosed with TB, or in those who come from areas with high endemicity. Occasionally, there may be symptoms of severe illness.

TB can affect multiple systems, but in the pediatric population, pulmonary TB is the most common, with lymph node involvement being predominant. Among extrapulmonary manifestations, tuberculous lymphadenitis and meningitis are the most frequent.

In most children, pulmonary TB results from the progression of a primary TB infection within the first year after infection, with involvement of the hilar or mediastinal lymph nodes. This can spread to the lung parenchyma, compress adjacent bronchi, or affect the pleura because of a hypersensitivity reaction or the spillage of caseum into the pleural space. Young or immunocompromised children with disseminated TB present with a characteristic pulmonary pattern resembling millet seeds (miliary TB). In children older than 10 years, reactivation of a previous TB infection is more common, overlapping with adult TB, with posterior apical cavities.

The symptoms of pulmonary TB are similar to those of other respiratory infections, including cough, sputum production, and chest pain, which develop insidiously and respond poorly to standard treatments. It is usually

accompanied by constitutional symptoms such as fever, night sweats, and weight loss. Large intrathoracic lymph nodes can cause respiratory distress with stridor and wheezing due to bronchial obstruction. Children with miliary involvement may present with hypoxemia. However, it is important to note that many children in low-prevalence settings, such as Spain, are asymptomatic or have very mild symptoms.

## Diagnosis

**Pediatric tuberculosis requires a systematic evaluation, including a focused medical history, physical examination, and assessment of risk factors and exposures. The tuberculin skin test is the initial screening method, supplemented by IGRA in specific situations to improve diagnostic yield. Imaging tests—X-ray, ultrasound, CT, or PET/CT—help define the extent and complications. Microbiological diagnosis using gastric juice, induced sputum, and molecular techniques is essential, although limited by the low bacterial load in children. The differential diagnosis should consider common respiratory infections, inflammatory, neoplastic, and granulomatous processes that can mimic TB. The primary care pediatrician is essential in the initial detection of pediatric tuberculosis through a careful medical history, physical examination, and basic tests, referring to specialized units when there is diagnostic uncertainty or a high suspicion of tuberculosis.**

The diagnostic evaluation that should be followed after exposure to TB is outlined in the algorithm at the end of the article.

## Medical history

- Look for the source of infection in the child's usual environment. If this exists, confirm the duration of exposure, the date of the last exposure, and whether the contact is bacilliferous and study of resistances.
- BCG vaccination and date. Number of doses and post-vaccination scar.
- Previous TST/IGRA, date of performance and result (millimeters of induration in 48-96 h).
- Previous existence of fever, lymphadenopathy, constitutional or respiratory symptoms.

- Report immunodeficiencies, diseases, or immunosuppressive therapy.

## Physical examination

It is usually normal, although it is possible to find evidence of pulmonary (wheezing, hypoventilation) or extrapulmonary (affectation of the VI cranial nerve, neck stiffness, arthritis, adenitis, etc.) manifestations.

## Tuberculin skin test (TST) or Mantoux intradermal reaction

It is the test of choice for screening. The goal of the TB test is to identify children infected with MTB in order to: 1) diagnose cases of TB disease; 2) detect infection early to prevent progression to disease; and 3) monitor exposed but uninfected children. It takes 8-12 weeks after infection for the TB test to become positive, reflecting the development of cellular immunity against MTB.

The test involves the intradermal administration of tuberculin or PPD (purified protein derivative), which contains over 200 antigens common to MTB, BCG, and other nontuberculous mycobacteria (NTM). If the child has previously been exposed to the bacillus, a delayed hypersensitivity reaction, known as the Mantoux test, will occur. A positive result only indicates infection; further testing is necessary to rule out active disease.

- *Technique:* store the tuberculin at 4°C, protected from light. Perform an intradermal injection on the anterior aspect of the forearm using a 26-gauge needle with a short bevel facing upwards: 0.1 mL/2 IU of PPD-RT23. A 6-10 mm wheal should develop.
- *Reading:* the reading should be taken at 72 hours, when maximum induration is reached, although it is possible to read it between 48 and 96 hours. The maximum induration diameter is measured transversely to the long axis of the arm (e.g., 15 mm; not 15 x 10 mm), always recorded in millimeters, with the date of the reading and the signature of the responsible person. If there is no induration, 0 mm of induration should be recorded, not negative. Blistering and necrosis are considered a positive result.

• *Interpretation:*

1. An induration  $\geq 5$  mm is considered **positive** in:
  - a. Children in close contact with the index case or suspected TB case.
  - b. Children suspected of having a clinical or radiological disease.
  - c. Children in situations of immunosuppression or HIV infection.
  - d. Children with conversion of a previously negative TST.
2. An induration  $\geq 10$  mm is considered **positive** in all other cases, including immigrant children, travelers, and screening of healthy children, regardless of whether there is a history of BCG vaccination.

TST can have false positives and negatives (Table I). Although not yet available, new intradermal tests based on MTB-specific antigens (ESAT6 and CFP10), with greater specificity, may be an alternative in the future<sup>(8)</sup>.

**Interferon-gamma Release Assays (IGRA)**

They detect the production of interferon-gamma by T cells in contact with the antigens ESAT-6 (Early Secretory Antigenic Target-6) and CFP-10 (Cul-

	<i>Population</i>	<i>Recommendation</i>
<b>Tuberculosis infection screening<sup>a</sup></b>	Children under 2 years old (to be assessed in children under 5 years old). Immunocompromised patient	Simultaneous TST + IGRA <sup>b</sup>
	Children over 5 years old who are not immunocompromised	TST or IGRA; if history of BCG vaccination or NTM infection, preferably IGRA
<b>Suspected TB disease</b>	All	TST or IGRA; if the result is negative, perform the other technique to maximize sensitivity <sup>b</sup> .

<sup>a</sup> Contact tracing, screening of immigrant population, screening prior to immunosuppressive treatment and immunocompromised patient.  
<sup>b</sup> Interpretation of discordant results: In high-risk patients (newborn, child under 5 years of age, immunocompromised or about to receive immunosuppressive treatment, known and recent intense exposure, suspected disease), *Mycobacterium tuberculosis* infection should always be considered. In low-risk patients, positive TST/negative IGRA: If there is a history of BCG vaccination or NTM infection, the IGRA could be repeated at 6-8 weeks, and the patient should be considered uninfected if it remains negative. Negative TST/positive IGRA: Confirm the appropriateness of the TST technique. IGRA: Interferon Gamma Release Assays; NTM: Nontuberculous Mycobacteria; TST: Tuberculin skin test.

ture Filtrate Protein-10). These antigens are present in the MTB group and, therefore, in wild-type strains of *M. bovis*, but not in the attenuated strain of the BCG vaccine, nor in most atypical mycobacteria (although they are present in *M. kansasii*, *M. marinum*, *M. szulgai*, and *M. flavescens*). Consequently, IGRAs are more specific than the TST

for diagnosing MTB infection, as they do not produce false positives due to BCG vaccination or most NTM<sup>(9)</sup>. Currently, two IGRAs are commercially available: QuantiFERON®-TB Gold Plus and T-SPOT®.TB.

Recommendations for the use of TST and IGRA techniques are included in table II.

<i>False negatives</i>	<i>False positives</i>
<ul style="list-style-type: none"> <li>- Window period (&lt;12 weeks)</li> <li>- Disseminated tuberculosis (meningitis, miliary tuberculosis, etc.)</li> <li>- Coinfection with the human immunodeficiency virus (HIV)</li> <li>- Measles infection, mumps, chickenpox, influenza, typhoid fever, brucellosis, typhus, leprosy, and whooping cough</li> <li>- Parasitic infections in the last 2 months</li> <li>- Live attenuated vaccines: MMR, oral polio, varicella, oral typhoid, and yellow fever</li> <li>- Immunosuppressive therapy</li> <li>- Neoplastic disease of lymphoid organs</li> <li>- Chronic kidney failure</li> <li>- Malnutrition</li> <li>- Newborns and the elderly</li> <li>- Injection too deep, expired antigen, incorrect dilution, improper storage, misreading, and left &gt;30 minutes in the syringe</li> </ul>	<ul style="list-style-type: none"> <li>- Infection by other nontuberculous mycobacteria</li> <li>- Calmette-Guérin Bacillus (BCG) vaccination</li> <li>- Misreading</li> </ul>

**Blood analysis**

It is usually nonspecific. Mild anemia, leukocytosis, and an elevated ESR (erythrocyte sedimentation rate) are common (a useful parameter for monitoring disease progression). Liver function tests are recommended before starting treatment.

**Radiological or visualization studies**

- **Chest X-ray:** it is not pathognomonic. It is possible to find forms with lymphadenopathy, atelectasis, pneumonia, cavitation (adolescents), micronodules (miliary), and any other pattern. A normal chest X-ray does not rule out TB.
- **Computed tomography (CT):** pathological lymph nodes measuring >5-10 mm with central hypodensity

and peripheral contrast enhancement can be visualized. CT is recommended in children with equivocal radiological findings, symptomatic patients with normal chest X-rays, in cases of diagnostic uncertainty in at-risk groups, for the assessment of complications in endobronchial TB, and in the follow-up of complex cases.

- **Lung ultrasound:** it allows visualization of consolidations, cavitations, and miliary nodules, provided the changes are in contact with the pleura. In expert hands, it has greater sensitivity than radiography for detecting mediastinal lymphadenopathy. It is also useful in the diagnosis of pleural effusion, abdominal lymphadenopathy, or focal splenic lesions.
- **Positron emission tomography associated with CT (PET/CT):** it allows differentiation of tuberculous disease from infection and residual images, evaluate the extent of the disease, monitor the response to treatment and identify foci of disease that are candidates for biopsy, but it has a higher degree of irradiation than CT, so its use should be restricted to selected cases.

## Microbiological studies

### Samples

In children unable to expectorate, the sample of choice for diagnosing pulmonary TB is gastric aspirate, collected on an empty stomach first thing in the morning during three consecutive days via nasogastric tube (obtain a minimum of 3–4 mL of gastric juice, inject 3 mL of sterile water, aspirate it, and add it to the sample), or induced sputum, which has similar sensitivity and is obtained by administering inhaled salbutamol followed by 3–10 mL of 3% hypertonic saline, nebulized for 15 minutes. The greatest diagnostic yield is achieved by collecting both induced sputum and gastric juice on the same day.

In adolescents or older children with a productive cough, sputum should be collected, and in intubated patients, bronchial aspirate or bronchoalveolar lavage should be obtained. Addition-

ally, in young children, stool analysis is recommended to increase diagnostic yield. Bronchoscopy and bronchoalveolar lavage for sample collection may be indicated in certain cases (diagnostic uncertainty, immunocompromised patients, slow disease progression, suspected drug-resistant TB). Similarly, if an endobronchial granuloma is suspected due to bronchial obstruction (extensive pulmonary atelectasis is present), rigid bronchoscopy for granuloma excision and histopathological examination is indicated.

### Techniques

- **Staining:** acid-fast bacilli smear microscopy (AFB) or direct visualization using auramine fluorescence or Ziehl-Neelsen staining. Sensitivity in children is between 10–15%. It is not specific, especially in patients at risk of infection with atypical mycobacteria.
- **Culture:** it is the reference technique. It allows identification of the species and phenotypic studies of resistance to antituberculosis drugs, but its sensitivity is low (30–50%) and it takes between 2 and 4 weeks to obtain the definitive result.
- **Molecular techniques, polymerase chain reaction (PCR) and massive sequencing:** although they do not replace culture as the gold standard, these tests have similar sensitivity, high specificity in children, and provide results within a few hours. The most widely used technique is Xpert<sup>®</sup>MTB/RIF Ultra (Cepheid, USA), which allows for the simultaneous detection of rifampicin resistance. In addition, there are massive parallel sequencing techniques, such as Deeplex<sup>®</sup>Myc-TB (Genoscreen, France), which allow for species identification, detection of resistance to antituberculosis drugs, and phylogenetic tracing for improved control of population transmission.
- **Molecular methods for detecting resistance:** the gold standard for studying sensitivity to antituberculosis drugs is culture; however, rapid molecular tests have been developed for detecting resistance-associated mutations, which have the great

advantage of speed, high sensitivity (90–97% if smear microscopy is positive, 67% if smear microscopy is negative), and specificity (99%). Besides Xpert<sup>®</sup>MTB/RIF Ultra, the most commonly used in our setting are those that detect resistance mutations to isoniazid and rifampicin, such as BD MAX<sup>®</sup>MDR-TB (BD, USA), Genotype<sup>®</sup>MTBDRplus (Hain Lifescience, Germany), or FluoroType<sup>®</sup>MTBDR (Hain Lifescience, Germany), and second-line drugs, such as Xpert<sup>®</sup>MTB/XDR (Cepheid, USA) or GenoType<sup>®</sup>MTBDRsl (Hain Lifescience, Germany)<sup>(10)</sup>.

### Others

- **Histological study of biopsy:** caseating and necrotizing granulomas.
- **Adenosine-Deaminase (ADA):** normal values are considered to be <40 U/L in pleural fluid and 1–4 U/L in cerebrospinal fluid. Elevated ADA levels are suggestive of tuberculosis, although not specific, as they can also increase in other effusions (empyemas, lymphomas). It has a high negative predictive value, so it is exceptional for an effusion with ADA <40 U/L to be tuberculous.
- **New diagnostic techniques:** in recent years, diagnostic tests are being developed using easily accessible samples, such as molecular techniques in capillary blood or biomarkers in saliva and urine, which are not yet available in our environment<sup>(11,12)</sup>.

## Differential diagnosis

The differential diagnosis of pulmonary tuberculosis in children is broad due to the nonspecific nature of its clinical manifestations, which often overlap with other common childhood respiratory infections. Conditions such as common bacterial pneumonias, especially those caused by *Streptococcus pneumoniae* and *Staphylococcus aureus*, persistent viral infections (adenovirus, influenza, SARS-CoV-2), *Mycoplasma pneumoniae* infection, and prolonged bronchitis should be considered. Hilar or mediastinal lymphadenopathy can be confused with processes such as lymphomas, fungal infections (histoplas-

Table III. Recommended doses of first-line antituberculosis drugs

	Daily dosage expressed in mg/kg/day (dose range)	Maximum daily dose (mg)
Isoniazid (H)	10 (7-15) <sup>a,b</sup>	300
Rifampicin (R)	15 (10-20) <sup>a</sup>	600
Pyrazinamide (Z)	35 (30-40)	2,000
Ethambutol (E)	20 (15-25) <sup>c</sup>	2,500

<sup>a</sup> Higher doses of isoniazid and rifampicin are used in tuberculous meningitis.

<sup>b</sup> Add pyridoxine 15-50 mg/day (maximum 50 mg/day) if exclusively breastfeeding, vegetarians, nutritional disorders, HIV and pregnant adolescents.

<sup>c</sup> It is recommended that, during the induction period of the disease, ethambutol be used at a bactericidal dose of 20-25 mg/kg/day, and during the maintenance period, decrease to 15-20 mg/kg/day.

Modified from: Working Group on Tuberculosis and Infection by other Mycobacteria of the Spanish Society of Pediatric Infectious Diseases. Consensus document on the treatment of pulmonary tuberculosis in children (2018).

Table IV. Commercially available first-line antituberculosis drug preparations in Spain

Isoniazid	<b>Cemidón B6®:</b> – Tablets: 50 mg, 150 mg and 300 mg – Vial for intravenous administration: 300 mg
Rifampicin	<b>Rifaldin®:</b> – Capsules: 300 mg – Suspension: 20 mg/mL – Vial for intravenous administration: 600 mg <b>Rimactan®:</b> – Coated tablets: 300 mg
Pyrazinamide	<b>Pyrazinamide Prodes®:</b> – Tablets: 250 mg
Ethambutol	<b>Myambutol®:</b> – Tablets: 400 mg
<b>Fixed-dose combination drugs (FDCs)</b>	
HR	<b>Rifinah®:</b> – Coated tablets: H 150 mg + R 300 mg
HRZ	<b>Rifater®:</b> – Coated tablets: H 50 mg + R 120 mg + Z 300 mg
HRZE	<b>Rimstar®:</b> – Coated tablets: H 75 mg + R 150 mg + Z 400 mg + E 275 mg

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

Modified from: Working Group on Tuberculosis and Infection by other Mycobacteria of the Spanish Society of Pediatric Infectious Diseases. Consensus document on the treatment of pulmonary tuberculosis in children (2018).

mosis), congenital malformations, or granulomatous diseases. In cases with prolonged fever and systemic involvement, entities such as atypical Kawasaki disease, autoimmune processes, or chronic inflammatory conditions should be

evaluated. Careful evaluation of epidemiology, risk factors, clinical progress, radiology, and immunological or microbiological tests is essential to guide diagnosis and differentiate tuberculosis from other more prevalent causes.

## Treatment

The management of pediatric tuberculosis includes isoniazid prophylaxis in exposed children without infection—those under 5 years of age or immunocompromised—followed by a repeat TST/IGRA at 8-12 weeks to determine whether to continue treatment and to implement temporary measures to reduce transmission. Children with tuberculosis infection should receive preventive treatment with various effective regimens (6H/9H, 3HR, or 4R), avoiding rifampin in those coinfecting with HIV and monitoring for potential hepatotoxicity. Tuberculosis disease requires a standard 6-month regimen (2HRZ(E)/4HR), with shorter alternatives for non-severe cases and adjustments for immunocompromised individuals or special situations, along with close monitoring of adherence, liver toxicity, and microbiological negativity. Prevention is based on contact tracing, BCG vaccination in at-risk groups, and addressing social determinants of health. The primary care pediatrician plays an essential role in early detection, therapeutic supervision, and monitoring of household contacts.

### Exposure to TB without infection (Tables III-V)

Initiate isoniazid prophylaxis in:

- All children under 5 years old.
- Children of any age with immunosuppressive treatment (prolonged use of corticosteroids, anti-TNF-alpha, immunosuppressant drugs, etc.) or comorbidities of the immune system (HIV, chronic renal insufficiency, solid or hematological tumors, primary immunodeficiencies, etc.).

Eight to twelve weeks after the last risky contact, a new TST will be performed, regardless of whether therapy was received. The procedure will be based on the results:

- If the second TST is < 5 mm (or IGRA negative, if performed) in the absence of clinical symptoms: discontinue preventive treatment, if initiated. In HIV-infected children, given the anergy, it is prudent to consider all those exposed as infected and treated as having an TB infection. Temporarily, it is important to try to reduce transmission by minimizing contact with sputum-positive individuals as much as possible, usually until completing two weeks of appropriate treatment.

Table V. Compounded Antituberculosis Drug Formulations. Compounding Project

	<b>Formulation</b>	<b>Precautions</b>	<b>Validity period</b>	<b>Conservation</b>
<b>Isoniazid</b> 10 mg/ml, oral solution	– Isoniazid 1 g – Sorbitol 70% (50 ml solution) – Preservative water 100 ml	Sorbitol (0.35 g/ml), methylparaben and propylparaben	30 days	– Fridge – Protected from light and air
<b>Isoniazid</b> 50 mg/mL, oral solution	– Isoniazid 5 g – Sorbitol 70% (50 L solution) – Preservative water 100 mL	Sorbitol (0.35 g/mL), methylparaben and propylparaben	30 days	– Fridge – Protected from light and air
<b>Pyrazinamide</b> 100 mg/mL, oral suspension	– Pyrazinamide 10 g – Syrup 100 mL	Contains sucrose (0.8 g/mL)	30 days	– Refrigerator or room temperature – Protect from light – Shake before use
<b>Ethambutol</b> 50 mg/mL, oral solution	– Ethambutol 5 g – Citric acid monohydrate 0.3 g – Sterile water 30 mL – Syrup 100 mL	Contains sucrose (0.6 g/mL)	30 days	– Ambient temperature – No need to shake

Source: reference<sup>(13)</sup>. Modified from: Working Group on Tuberculosis and Infection by other Mycobacteria of the Spanish Society of Pediatric Infectious Diseases. Consensus document on the treatment of pulmonary tuberculosis in children (2018).

In newborns of sputum-positive mothers, it is recommended to start isoniazid prophylaxis for at least 12 weeks, after ruling out infection and tuberculosis disease in the infant. When the second TST/IGRA is negative at 12 weeks, prophylaxis can be discontinued if the mother adheres well to the treatment or has completed it. It is recommended to repeat the TST/IGRA at 6 months and 1 year. The appropriateness of the BCG vaccine will be evaluated. Breastfeeding is not contraindicated, except in cases of tuberculous mastitis. It is recommended to express the milk and administer it in a bottle to avoid contact with the baby in the following cases: if the mother has received less than 2 weeks of therapy, if the mother remains bacilliferous despite treatment, or if the strain is not sensitive to first-line drugs.

- If the second TST is  $\geq 5$  mm (or positive IGRA, if performed): act according to section TBI.

### Treatment of tuberculosis infection

All children and adolescents diagnosed with TBI should receive treatment to prevent the progression of the disease, and it is essential to rule out active disease before starting treatment. Several regimens with similar efficacy exist<sup>(4)</sup>:

- **Isoniazid 6–9 months (6H or 9H).** In immunocompetent patients, the duration tends to be shortened to 6 months.
- **Isoniazid and rifampicin for 3 months (3HR).** Especially recommended in adolescents or if poor adherence is suspected.
- **Rifampicin 4 months (4R).** This regimen has demonstrated similar efficacy and safety to other regimens, while improving adherence.

In children co-infected with HIV, rifampicin regimens are not recommended; it is a crucial drug if they develop HIV and could become ineffective. Furthermore, rifampicin interacts with antiretrovirals, especially protease inhibitors, decreasing their levels and increasing rifampicin toxicity.

The low risk of hepatotoxicity in children makes routine transaminase monitoring inadvisable during TBI treatment, unless compatible symptoms, underlying liver disease, or concomitant hepatotoxic medication are present. In immigrants from countries endemic for viral hepatitis, HIV, or schistosomiasis, these conditions should be ruled out before initiating treatment.

### Treatment of tuberculosis disease

#### Classical regime

The standard TB treatment regimen is 6 months (2 months HRZ(E) +

4 months HR)<sup>(6)</sup>. Given the prevalence of H-resistant strains in Spain (>4%), E should be added in the intensive phase if disease caused by a first-line drug-susceptible strain has not been confirmed in the patient or index case.

In the first phase, the induction or bactericidal phase, there is a rapid decrease in the number of bacilli, with marked clinical improvement and a reduction in transmissibility. In the second phase, the maintenance phase, the elimination of quiescent bacilli occurs. When the strain's susceptibility is known and resistance is not present, three drugs can be administered during the induction phase (2 months HRZ + 4 months HR)<sup>(4)</sup>. This treatment achieves a cure in >95% of cases, with few adverse effects. All drugs should be taken together on an empty stomach. In patients at risk of non-adherence, immunocompromised patients, or those with resistant strains, directly observed therapy (DOT) is recommended<sup>(13)</sup>.

#### Short regimen in non-severe TB<sup>(14)</sup>

In children with non-severe TB, a short 4-month regimen (2 months HRZ(E) + 2 months HR) is recommended, provided the following criteria are met:

- Age over 3 months.
- Non-severe TB: Intrathoracic lymph node TB without airway obstruction; pulmonary TB limited to one lung lobe, without miliary pattern,

**Table VI. Child-friendly formulations in dispersible tablets of first-line antituberculosis drugs**

Formulations	Instructions
Isoniazid 100 mg	TBI and TB exposure
Ethambutol 100 mg	TB in induction phase
Isoniazid 50 mg + rifampicin 75 mg	TBI and TB in maintenance phase
Isoniazid 50 mg + rifampicin 75 mg + pyrazinamide 150 mg	TB in induction phase

*TB: tuberculosis; TBI: tuberculous infection.*

without cavities, with uncomplicated pleural effusion; and peripheral lymph node TB.

- Non baciliferous TB.
- No suspicion or evidence of drug-resistant TB.

Considerations and limitations to short regimes:

- Children and adolescents who do not meet the criteria for non-severe TB should receive standard 6-month treatment, or the regimens recommended for severe forms of extrapulmonary TB.
- Infants under 3 months should always receive a 6-month regime.
- Children and adolescents who have received TB treatment in the previous 2 years should be treated with the standard 6-month regimen (2HRZ(E)/4 HR).

- In immunocompromised patients, treatment is recommended for at least nine months (ideally 12 months), with an induction phase using four drugs until the strain's susceptibility is known in all children. In children living with HIV who are in optimal condition regarding their underlying disease, the general recommendations for immunocompetent patients should be followed; however, they should not receive less than nine months of treatment if the initial response or immune recovery is poor. Rifampicin interferes with protease inhibitors, so substitution with rifabutin should be considered; it can also interact with non-nucleoside reverse transcriptase inhibitors (efavirenz and nevirapine). These patients should always be referred to specialized units for management<sup>(15)</sup>.

In Spain, **child-friendly dispersible tablet formulations** of first-line antituberculosis drugs are available (as a foreign medicine) for the treatment of TB exposure, TBI and tuberculosis disease<sup>(16)</sup> (Table VI).

**Follow-up of the child with pulmonary TB (Table VII)**

In monitoring TB treatment in children, it is important to:

- **Monitor adherence, related problems, and dosage adequacy at each visit:** poor adherence is the most common cause of treatment failure. Sometimes, directly observed therapy or monitoring of plasma drug levels can be used to assess adherence.
- **Assess potential liver toxicity:** liver function tests should be performed if signs or symptoms consistent with hepatitis appear, if the patient is receiving other potentially hepatotoxic drugs, or if they have another condition that may cause hepatitis.
- **In baciliferous patients** (usually adolescents): bacilloscopy should be repeated periodically (every 1-2 weeks) until it is negative, which allows the end of respiratory isolation.
- At least one **clinical check-up** should be performed 2 weeks after the start of treatment, two months to move to the maintenance phase and, subsequently, every two months until the treatment is completed.

**Table VII. Follow-up of the child with pulmonary tuberculosis under treatment**

	At diagnosis	2 weeks	1 month	2 months	6 months
Clinical check-up	X	X	X	X	X
Therapeutic compliance	X	X	Consider withdrawing the 4th drug	Pyrazinamide withdrawal	End of treatment
Complete blood count and erythrocyte sedimentation rate (ESR)	X	Note a	Note a	Note a	Note a
Transaminases, bilirubin, urea, creatinine, and uric acid	X	Note a	Note a	Note a	Note a
Sputum/induced sputum/gastric juice	X	Note b	Note b		
Chest X-ray	X			Note c	

*Notes: a: They will only be repeated in special cases (according to clinical findings, previous analytical alteration, immunocompromised patients, infants, concomitant use of drugs with possible toxicity); b: In patients with previous positive bacilloscopy; c: In case of paradoxical reaction, consider performing another radiographic control after completing treatment with corticosteroids, if administered. General note: additional tests and visits will be carried out as necessary according to the patient's clinical condition and characteristics.*

**Hospital admission criteria**<sup>(17)</sup>

- <2 years.
- Severe pulmonary forms (pleural effusions, atelectasis, etc.).
- Severe or disseminated forms.
- Extrapulmonary forms, except for isolated lymph node involvement.
- Baciliferous forms (adolescent with caverns).
- Suspected drug-resistant disease.
- Previous therapeutic failure (after at least 2 months).
- Suspected or at risk of therapeutic non-compliance.
- Immunocompromised.
- Sample collection.

**Treatment in specialized TB units**

The treatment and follow-up of immunocompromised children, with resistant TB, with complex forms or with risk factors for complications, or with poor response to treatment, will be carried out in expert units, with experience in this pathology<sup>(4)</sup>.

**Paradoxical reaction**

During the first 2 months of treatment, a paradoxical reaction may occur in 5-10% of cases, characterized by clinical and radiological worsening. In these cases, oral corticosteroids, 2 mg/kg/day of prednisone or equivalent, will be added for 3-4 weeks, with a gradual taper over 2 weeks<sup>(4)</sup>.

**Adverse reactions**

The most frequent side effect is hepatic toxicity from isoniazid, rifampicin, or pyrazinamide, although it is most characteristic of isoniazid. In cases of mild hepatotoxicity, the isoniazid dose should be adjusted to 5 mg/kg/day. If the patient develops symptoms with transaminase levels above three times the upper limit of normal or is asymptomatic with levels above five times the upper limit of normal, treatment and any other hepatotoxic drugs should be discontinued. The etiological workup for hepatitis should be completed, and liver function should be monitored. When the transaminase levels are below twice the upper limit of normal and clinical symptoms have resolved, rifampicin and ethambutol should be reintroduced initially. If liver function remains stable after 3-7 days, isoniazid can be reintroduced, and monitoring should

continue after 3-7 days. Pyrazinamide should never be reintroduced. In the event of a further deterioration of liver function, a new therapeutic regimen should be designed in a specialized unit. As for ethambutol, the most frequent side effect is optic neuritis, which will lead to discontinuing the drug, although it is usually reversible.

**Prevention**

Tuberculosis prevention in children combines strategies aimed at preventing infection and stopping its progression to disease. Early identification and contact tracing allow for the detection of exposed children and the provision of preventive treatment, when necessary, especially in children under 5 years of age and in immunocompromised individuals. BCG vaccination remains key in countries with high endemicity and in at-risk groups, as it reduces severe forms, such as disseminated TB and meningitis. In addition, improved socioeconomic conditions, adequate access to health services, and control of transmission in community and school settings contribute significantly to reducing incidence<sup>(18-20)</sup>.

**Role of the Primary Care Pediatrician**

The primary care pediatrician plays a key role in the initial suspicion of pediatric TB. It is essential that they conduct a thorough medical history and physical examination, as well as order the available first level tests (TST and chest X-ray). If, after this initial assessment, there is a high suspicion of tuberculosis, the patient should be referred to specialized units for further evaluation, collection of microbiological samples, and initiation of treatment.

The primary care pediatrician also plays an essential role in follow-up after the start of treatment. Monitoring side effects and ensuring proper adherence are crucial for the patient's recovery and for curbing transmission. This follow-up should also be carried out in the case of exposed patients, in whom the absence of infection or disease must be confirmed once the window period (8-12 weeks) has passed. Furthermore, the primary care pediatrician can also

be involved in contact tracing for family members and other household members.

**Conflict of interest**

There is no conflict of interest in the preparation of this manuscript. Funding sources: PRM is funded by the Carlos III Health Institute – Spanish Ministry of Health and EU Feder funds (Juan Rodés Contract JR24/00015).

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## Clinical case

**Reason for consultation:** close contact with a bacilliferous patient diagnosed with pulmonary tuberculosis (TB).

**History:** a 13-month-old boy of Spanish origin was referred for evaluation due to close contact with his caregiver, who was diagnosed with smear-positive pulmonary tuberculosis. The child is asymptomatic. The caregiver is a 35-year-old woman from the Philippines who has resided in Spain for the past two years. She has a three-month history of cough with expectoration. A chest X-ray revealed a cavity in the right upper lobe. Sputum analysis was performed: positive smear microscopy; PCR (Xpert Ultra): positive (no resistance mutations to R); and culture yielded a susceptible strain. The care provider lives with her husband and their two children, ages 14 and 9.

**Personal background:** this is a healthy 13-month-old boy with no relevant medical conditions. He took antireflux medication (ranitidine) until 3 months of age and is currently off treatment. His psychomotor development is normal. He was born in Spain and has not received the BCG vaccine.

**Full physical examination:** no alterations.

**Additional tests:** the following tests were performed at his health center: tuberculin skin test: 8 mm; and chest x-ray: hilar lymphadenopathy. He was referred to a specialized TB unit for further evaluation: blood work with liver profile: normal; gastric juice analysis: negative bacilloscopy; PCR (Xpert

Ultra): positive (no R resistance mutations); culture pending; PCR (Xpert Ultra) in stool: negative.

**Diagnosis:** tuberculosis disease.

**Treatment:** given that the patient meets the criteria for non-severe TB and the index case strain is drug-sensitive, a short, four-month treatment course can be administered. Treatment is initiated with three drugs, as the index case strain's sensitivity is known: H+R+P for two months, followed by H+R for two months. A request is made to a foreign pharmaceutical company for orally dispersible formulations to facilitate administration. The patient must take all drugs together every morning on an empty stomach. The family is informed that the medication may cause bodily fluids to turn orange. They are also advised that the index case must remain in isolation until at least two weeks of treatment have been completed and sputum smear microscopy has shown a negative result.

**Follow-up:** the patient is jointly monitored by his primary care pediatrician and the specialized TB unit. Visits are scheduled two weeks after the start of treatment, at two months, and at four months. At each visit, adherence to treatment is confirmed, and the dose is adjusted according to weight. At two months, pyrazinamide is discontinued, and isoniazid and rifampin are continued until the four-month treatment course is completed. Contact tracing is conducted among the caregiver's household members (husband and two children).

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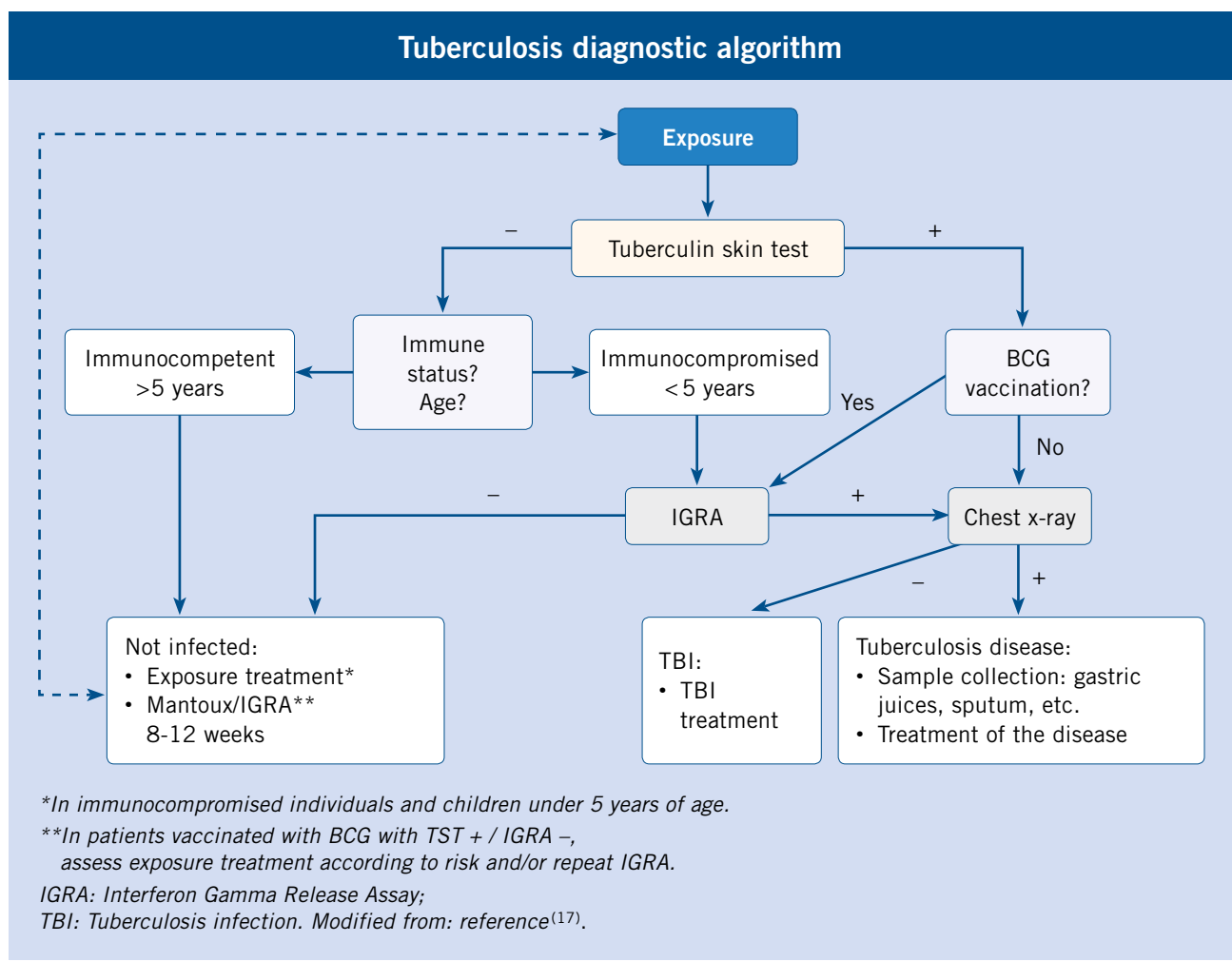
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Consensus article and update on the diagnosis and treatment of pediatric TB, which brings together the vision of pediatricians who are experts in its management.

- Turkova A, Wills GH, Wobudeya E, Chabala C, Palmer M, Kini-kar A, et al. Shorter Treatment for Non severe Tuberculosis in African and Indian

Children. *N Engl J Med*. 2022; 386: 911-22. Available at: <https://doi.org/10.1056/nejmoa2104535>.

The first clinical trial conducted specifically in a pediatric population has demonstrated that children with non-severe tuberculosis can be effectively treated with a shorter, 4-month regimen, instead of the traditional 6 months. This represents a potential shift in global clinical practice, as it shortens the duration of treatment without compromising efficacy or safety, reduces the risk of treatment discontinuation, lessens the burden on families and healthcare systems, and facilitates the expansion of directly observed treatment strategies.



## Accreditation quiz

The Accreditation Questionnaires for FC topics can be done at “On line” through the web: [www.sepeap.org](http://www.sepeap.org) and [www.pediatriaintegral.es](http://www.pediatriaintegral.es). To obtain the single continuous training accreditation from the accreditation system for health professionals for the entire national health system, 70% of the questions must be answered correctly. The accreditation questionnaires on the different issues in the journal may be carried out during the period stated in the online questionnaire.



# Accreditation quiz

Subsequently, the following accreditation quiz of *Pediatría Integral* collects questions on this topic, which must be answered online through the website: [www.sepeap.org](http://www.sepeap.org).

In order to obtain certification by the Spanish “formación continuada” national health system for health professionals, 70% of the questions must be answered correctly. The accreditation quizzes of the different numbers of the journal may be submitted during the period indicated in the “on-line” quiz.

## Pulmonary tuberculosis

17. What is the MOST COMMON radiological finding in pulmonary tuberculosis in children?

- Pulmonary cavitations.
- Hilar or mediastinal lymphadenopathy.
- Pleural effusion.
- Apical infiltrates.
- None of the above.

18. WHICH of the following is a treatment guideline for tuberculosis infection in a child with no additional risk factors?

- Isoniazid and rifampicin for 6 months.
- Isoniazid and rifampicin for 3 months.
- Isoniazid for 4 months.
- Isoniazid, rifampicin, pyrazinamide and ethambutol for 2 months.
- All of the above are equally effective.

19. In what cases is the tuberculin skin test and IGRA (Interferon-Gamma Release Assays) indicated?

- In children vaccinated with BCG, in <5-year-olds and in immunocompromised individuals.
- In children with symptoms consistent with tuberculosis.
- In children vaccinated with BCG, in those under 10 years of age, and in malnourished children.
- In children with radiographic abnormalities consistent with tuberculosis.

e. In children diagnosed with tuberculosis disease to monitor the response to treatment.

20. Which patient is LEAST vulnerable to developing tuberculosis?

- A refugee child from Ukraine.
- Adolescent in treatment with infliximab.
- A 17-month-old child who attends daycare.
- A child who travels frequently to visit his family in Morocco.
- A teenager who travels to the United States to study.

21. What is the most frequent cause of tuberculosis treatment failure in children?

- Liver toxicity.
- Poor adherence.
- Eye toxicity.
- Tuberculosis resistant to first-line drugs.
- Gastrointestinal toxicity.

## Clinical case

22. The patient in the clinical case has been classified as a patient with TB disease. What is the MAIN difference between exposure, infection, and tuberculosis disease in children?

- Exposure involves clinical and radiological symptoms, whereas infection does not.
- In latent infection, children present with bacilli in sputum, but no transmission.
- The disease presents clinical symptoms but is no longer transmissible.
- Exposure involves contact with the bacillus without infection;

the infection is asymptomatic without transmission; the disease presents symptoms and is transmissible.

e. The patient in the clinical case should be classified as having a tuberculous infection, since he is asymptomatic.

23. Our patient has a tuberculin skin test of 8 mm. What does this result mean?

- That result means that the tuberculin skin test is negative, since it is below 10 mm.
- The result is positive and indicates lung disease due to *Mycobacterium tuberculosis*.
- Tuberculin allergy.
- Meningeal tuberculosis.
- In this patient, the result should be considered positive and indicates previous exposure to *Mycobacterium tuberculosis*.

24. In the case at hand, has the short 4-month treatment regimen (2 HRZE + 2 HR) been applied CORRECTLY?

- No, because he is an infant under one year old and this should not be applied.
- Yes, because when obtaining a PCR test in the patient without resistance mutations to rifampicin, the short course can be applied even if the culture result is not available.
- Yes, because it meets the non-severe tuberculosis criteria and the index case strain is sensitive.
- No, because we do not have the results of the culture.
- Yes, since the tuberculin skin test is less than 10 mm.