

# Tuberculosis in Children: Challenges in Diagnosis and the Decision to Treat

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## Abstract

Tuberculosis in children, especially younger children, is challenging. Symptoms are often non-specific, and the clinical and radiographic manifestations are similar to those of several other infectious diseases. Pediatricians play an important role in this process by raising awareness about tuberculosis in childhood, guarantying a prompt diagnosis, using all available laboratory tools, and ensuring adequate treatment. New guidelines have recently published the advocated changes in diagnosis methodology and drug treatment regimens and increased the chance of microbiological confirmation and treatment success accordingly. Although the discovery of each new pediatric case means a decrease in associated mortality, the focus should be primarily on identification of each child as a contact with an adult with active tuberculosis and provision of preventive treatment.

**Keywords:** Adolescent; Child; Clinical Decision-Making; Portugal; Tuberculosis/diagnosis; Tuberculosis/drug therapy

Tuberculosis (TB) remains one of the 20 leading causes of death worldwide. Children accounted for 11% of all reported cases in 2020, and 53%, 32%, and 16% of all cases of deaths among human immunodeficiency virus-negative people were male, female, and children (aged < 15 years), respectively. The challenges in the diagnosis and the increased risk of mortality and morbidity in children are well recognized.<sup>1</sup>

Children, especially those under the age of 6, are more susceptible to infection. The risk of progression to disease, when infected and untreated, can be as high as 40% in the first year of life, and the risk of meningeal or miliary tuberculosis is up to 20%.<sup>2</sup>

The diagnosis of active tuberculosis in children is a challenge. Suspicion is raised by symptoms such as cough and/or persistent fever or identification of a child who has been in contact with an active tuberculosis case. However, symptoms are often nonspecific, which leads to a delay in the diagnosis.<sup>3</sup>

Considering that pulmonary tuberculosis is the most frequent form of the disease, the investigation usually begins with a chest radiography. Miliary patterns, lymphadenopathies with or without airway compression, parenchymal opacification, or even cavities may be observed, despite the absence of pathognomonic findings.<sup>4</sup>

Classically, the childhood disease presents paucibacillary forms, which decreases the likelihood of microbiological confirmation. However, obtaining specimens in order to confirm the disease should not be ignored, considering the importance of *Mycobacterium tuberculosis* drug susceptibility tests in the drug regimen options.<sup>5</sup>

Sample collection for suspected pulmonary tuberculosis is difficult. Gastric aspirate is the preferred method in children under 10 years old. Its yield, however, is about 50%, though it may be higher in those with disseminated forms or intrathoracic lymph node involvement. Gastric aspirate requires trained professionals and should be performed under fasting conditions. Moreover, it is invasive and less accepted by parents or caregivers. Induced sputum collection or nasopharyngeal aspirate can be combined with gastric aspirate to increase diagnostic accuracy. The World Health Organization (WHO) recommends obtaining stool samples, as an alternative technique. It is a non-invasive technique that can be performed at home, which makes it more acceptable for parents or caregivers.<sup>6</sup>

Another important laboratory tool for treatment is the use of molecular resistance test, which includes Xpert<sup>®</sup> MTB/RIF (Cepheid). The WHO recommends molecular testing in all patients, both on respiratory and non-respiratory specimens. Sensitivity is 65%,

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73%, and 61% in sputum, gastric aspirate, and stool, respectively. The Xpert ultra sensitivity has shown to be 73%, 64%, and 53% for sputum, gastric aspirate, and stool, respectively.<sup>6,7</sup>

The decision to treat is not always an easy one, and in children, should be made based on a combination of symptoms, imaging and microbiological findings, or even evidence of *Mycobacterium tuberculosis* infection based on immunological tests. The existence of decision algorithms in children under 10 years of age, published by WHO, may be used in countries with high incidence. Two algorithms have been published according to the availability or not of a chest radiography.<sup>5-8</sup>

The selected treatment regimen should always consider both bactericidal and bacteriostatic antibiotics. Rifampin (R) and isoniazid (H), due to their bactericidal effect, remain the mainstays in tuberculosis treatment. Pyrazinamide (Z) and ethambutol (E) complement the drug regimen. The former is bacteriostatic, and the latter prevents resistance and is a non-hepatotoxic drug. In children, the use of ethambutol has been recommended as the first-line drug regimen since 2014. Ophthalmologic effects are rare in children and are dose and time dependent. It should not be forgotten that there is a proportion of about 6% resistance to isoniazid in Portugal; therefore, it should be included in the initial treatment until susceptibility to isoniazid is known.<sup>9,10</sup>

Recently, the SHINE study concluded the efficacy of shorter treatment regimens in children with uncomplicated tuberculosis, between 3 months and 16 years of age. The recommendation is a four-month treatment option: two months with HRZ with or without ethambutol, followed by the maintenance phase with HR for two months.<sup>11,12</sup>

In severe forms, namely meningeal, osteoarticular, or miliary forms, 12 months of treatment is still recommended. However, in meningeal tuberculosis, a six-month drug regimen with HRZ and ethionamide has proven to be effective, with decreased mortality, despite a higher proportion of neurological sequelae among survivors.<sup>6,7</sup>

In Portugal, the number of new cases of tuberculosis has been decreasing and reached the threshold defined as low incidence (20 cases per 100 000 inhabitants per year) in 2015. Nevertheless, Portugal continues to be the Western European country with the highest rate of tuberculosis incidence.<sup>10</sup>

In 2020, 1465 cases of the disease were reported in Portugal (1848 cases in 2019), representing a reported rate of 14.2 per 100 000 habitats. The incidence rate among 0-5-year-olds was 4.78 cases per 100 000, while this rate was 8.66 cases per 100 000 in the same age group in 2019.<sup>10</sup>

Portugal has several strategies in place that have contributed significantly to the continuous decrease in tuberculosis incidence, including free access to tuberculosis centers, free screening, and treatment and strategies to promote successful treatment.<sup>10</sup>

The goals proposed by the WHO include the reduction of the number of tuberculosis deaths by 95% and the tuberculosis incidence rate by 90% by 2035. The identification of the most vulnerable ones, namely those with the highest risk of exposure, difficulties in accessing health care, and individuals at high risk of developing tuberculosis after exposure, is an important target that impacts the disease incidence.<sup>13</sup>

In 2021, Portugal has applied to the project Country Support for TB Elimination in Europe (ECDC/2019/030) promoted by the European Centre for Disease Prevention and Control to reinforce the strategies for tuberculosis control and elimination.<sup>14</sup>

The analysis of the strategies already implemented in Portugal for vulnerable populations in Portugal identified some challenges<sup>14</sup>:

1. Strategies in Portugal have been, so far, mostly focused on the identification of active tuberculosis cases, and it is now necessary to shift the focus on screening and preventive treatment for the most susceptible ones.
2. Tuberculosis health care exists and is free for all; however, the general population must know how to access tuberculosis healthcare services.
3. Epidemiological surveillance data must be systematically analyzed at national and regional levels.
4. There is insufficient funding and continuity of funding to sustain longer term tuberculosis care activities in vulnerable populations.
5. Strategies must be patient-centered and take local responses into consideration.

The Global Plan to Stop TB 2023-2030<sup>15</sup> reinforces the importance of placing tuberculosis in the sustainable development goals. The main milestones for the control and elimination of the disease include integrated patient-centered care with a multisectoral approach, engaging the different levels of health care and connecting the various stakeholders, caring for the most vulnerable, and providing universal access.<sup>15</sup>

The pediatrician plays a key role here considering the difficulties and challenges involved with confirmation of tuberculosis cases in children and the decision to treat. The existence of specialized centers with dedicated professionals and the existence of guidelines and procedures facilitates the diagnosis and the establishment of effective treatment. However, the importance of links with the community, stakeholders, other health care services, and public health services

cannot be forgotten, especially when it comes to screening and prevention of the disease in children.

### Conflicts of Interest

The author declare that there were no conflicts of interest in conducting this study.

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### Protection of human and animal subjects

The author declare that the procedures followed were in accordance with the regulations of the relevant clinical research ethics committee and with those of the Code of Ethics of the World Medical Association (Declaration of Helsinki 2013).

### Provenance and peer review

Commissioned; without external peer review.

### Confidentiality of data

The author declare that she has followed the protocols of her work center on the publication of patient data.

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### Tuberculose nas Crianças: Desafios no Diagnóstico e na Decisão de Tratamento

A tuberculose nas crianças é um desafio, especialmente nas crianças mais novas. Os sintomas geralmente são inespecíficos e as manifestações clínicas e radiográficas são semelhantes às de várias outras doenças infecciosas. Os pediatras desempenham um papel importante neste processo ao sensibilizar sobre a tuberculose na infância, garantindo o diagnóstico imediato, utilizando todos os meios laboratoriais disponíveis e garantindo o tratamento adequado. Novas diretrizes publicaram recentemente as mudanças preconizadas na metodologia de diagnóstico e nos regimes de tratamento medicamentoso e aumentaram

a probabilidade de confirmação microbiológica e sucesso do tratamento. Embora a descoberta de cada novo caso pediátrico signifique uma diminuição da mortalidade associada, o foco deve estar principalmente na identificação de cada criança como contato com um adulto com tuberculose ativa e no fornecimento de tratamento preventivo.

**Palavras-Chave:** Adolescente; Criança; Portugal; Tomada de Decisão Clínica; Tuberculose/diagnóstico; Tuberculose/tratamento farmacológico

