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REVIEW ARTICLE

Epidemiological aspects, clinical manifestations, and prevention of pediatric tuberculosis from the perspective of the End TB Strategy

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ABSTRACT

Tuberculosis continues to be a public health priority in many countries. In 2015, tuberculosis killed 1.4 million people, including 210,000 children. Despite the recent progress made in the control of tuberculosis in Brazil, it is still one of the countries with the highest tuberculosis burdens. In 2015, there were 69,000 reported cases of tuberculosis in Brazil and tuberculosis was the cause of 4,500 deaths in the country. In 2014, the World Health Organization approved the End TB Strategy, which set a target date of 2035 for meeting its goals of reducing the tuberculosis incidence by 90% and reducing the number of tuberculosis deaths by 95%. However, to achieve those goals in Brazil, there is a need for collaboration among the various sectors involved in tuberculosis control and for the prioritization of activities, including control measures targeting the most vulnerable populations. Children are highly vulnerable to tuberculosis, and there are particularities specific to pediatric patients regarding tuberculosis development (rapid progression from infection to active disease), prevention (low effectiveness of vaccination against the pulmonary forms and limited availability of preventive treatment of latent tuberculosis infection), diagnosis (a low rate of bacteriologically confirmed diagnosis), and treatment (poor availability of child-friendly anti-tuberculosis drugs). In this review, we discuss the epidemiology, clinical manifestations, and prevention of tuberculosis in childhood and adolescence, highlighting the peculiarities of active and latent tuberculosis in those age groups, in order to prompt reflection on new approaches to the management of pediatric tuberculosis within the framework of the End TB Strategy.

Keywords: Tuberculosis, pulmonary/prevention & control; *Mycobacterium tuberculosis*; Lung diseases/etiology; Child; Adolescent.

INTRODUCTION

Tuberculosis is still one of the main causes of morbidity and mortality worldwide. The World Health Organization (WHO) estimates that, in 2016, there were 10.4 million new cases of tuberculosis, as well as that, in that same year, tuberculosis caused the deaths of 1.3 million non-HIV-infected individuals and 374,000 HIV-infected individuals. Also in 2016, tuberculosis was one of the ten leading causes of death worldwide, ranking above HIV/AIDS as the leading cause of death from a single infectious agent.[1]

Children are particularly vulnerable to tuberculosis. Pediatric cases of tuberculosis account for 10% of all cases of the disease. In 2015, there were an estimated 1 million new cases of childhood tuberculosis and an estimated 210,000 deaths from tuberculosis in children.[2]

Despite the advances in tuberculosis control achieved in the last decade, our country still ranks among those with the highest tuberculosis burdens. In the new WHO classification of priority countries for tuberculosis control worldwide (comprising three lists of 30 countries each), Brazil ranked 20th regarding the burden of disease and 19th regarding the tuberculosis/HIV coinfection.[2,3] In 2015, 69,000 tuberculosis cases were reported in Brazil (4,500 of those cases resulting in death), 6,800 HIV-infected individuals were diagnosed with tuberculosis, and more than 1,000 individuals developed multidrug-resistant tuberculosis (MDR-TB) or extensively drug-resistant tuberculosis (XDR-TB).[3]

In 2014, the WHO approved The End TB Strategy, which is in alignment with the United Nations Sustainable Development Goals. The new strategy adopts the vision of "A world free of tuberculosis – zero deaths, disease and suffering due to tuberculosis" and has the goal of ending

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the global epidemic and eliminating tuberculosis in low-incidence countries. The goals, to be met by 2035, are a 90% reduction in the incidence rate and a 95% reduction in the number of deaths due to tuberculosis—both in comparison with the rates reported for 2015. The first translates to a reduction in the tuberculosis incidence rate to fewer than 10 cases/100,000 population, which would represent the end of tuberculosis as a public health problem and a major step forward in disease control worldwide. However, the complete elimination of tuberculosis, defined as below 1 case/100,000,000 population, is an even more ambitious goal. In order for these objectives of the End TB Strategy to be achieved, there must be effective control measures that are based on three pillars[3-6]: integrated, patient-centered tuberculosis care and prevention; bold policies and supportive systems; and intensified research and innovation related to tuberculosis.

Given the considerations listed above, the relevance of tuberculosis at the global, regional, and national levels becomes evident. However, the importance of tuberculosis as a cause of morbidity and mortality in individuals under 15 years of age and the peculiarities of its prevention, diagnosis, and treatment in that age group have only recently gained prominence in the international scientific community.[7] In this review, we present the main clinical and epidemiological aspects of tuberculosis in children, together with aspects related to its prevention, aiming to contribute to the discussion of interventions to be implemented in pediatric tuberculosis patients within the framework of the End TB Strategy.

EPIDEMIOLOGY

The occurrence of tuberculosis in children is closely related to the prevalence of tuberculosis among adults. The risk of developing infection with *Mycobacterium tuberculosis* is higher for children living in regions where there is a high prevalence of active tuberculosis, in dwellings with high population density (many people sleeping in the same room), and in buildings with poor ventilation.[8-10]

In 2016, new cases of tuberculosis notified among children accounted for 6.9% of all tuberculosis cases worldwide. In that same year, there were over a million estimated new cases of pediatric tuberculosis—550,000 (range, 340,000-760,000) among males and 490,000 (range, 300,000-680,000) among females—corresponding to 10% of all new tuberculosis cases worldwide. According to the WHO, the three regions where most pediatric tuberculosis cases are concentrated are Southeast Asia, Africa, and the Western Pacific, which respectively accounted for 35%, 30%, and 20% of the new cases reported in 2015.[1]

It is estimated that tuberculosis caused the death of 210,000 children worldwide in 2015,[2] although mathematical models indicate that the number could have reached 239,000, 80% (191,000) of those deaths having occurred in children under 5 years of age in Africa and Southeast Asia.[11] Based on those estimates, Dodd et al.[11] stated that tuberculosis might be the sixth leading cause of death in the 1- to 5-year age group, causing more deaths than do diseases such as meningitis, AIDS, measles, and whooping cough.

The mortality associated with tuberculosis among children who go untreated has been estimated to be 21.9% overall and 43.6% among those under 5 years of age. However, it has been reported that such mortality can be reduced to 0.9% when tuberculosis treatment is carried out properly.[12] Mortality due to tuberculosis in children is underestimated, because, for many children who die from tuberculosis, the cause of death is listed as pneumonia, HIV/AIDS, meningitis, or malnutrition.[13,14]

There are no official estimates of the prevalence of latent tuberculosis infection (LTBI) among children, because there are no accurate diagnostic tests. However, in a study using mathematical modeling,[11] it was estimated that the number of children with LTBI worldwide in 2010 was 53,000,000 (95% CI: 41,000,000-69,000,000).

NATURAL HISTORY OF TUBERCULOSIS IN CHILDREN

Approximately 90% of people do not become ill after primary infection with *M. tuberculosis*, subsequently developing LTBI.[15-17] However, children are at a higher risk of rapid progression from tuberculosis infection to active tuberculosis and more often develop the extrapulmonary or disseminated forms of the disease. The risk of active tuberculosis is highest in children under 5 years of age, and recent evidence suggests that children can become infected after only 15-20 min of exposure to *M. tuberculosis*.[17-20] After *M. tuberculosis* infection, the disease can manifest at any time in life, depending on the balance between the pathogen and the host immunity, especially cellular immunity, although most children will develop active tuberculosis within a year after becoming infected. That is why determining the history of contact with cases of pulmonary tuberculosis (PTB) is so important and reveals the maintenance of tuberculosis transmission within the community.[17]

The differences between the pediatric and adult populations in terms of the pathophysiology and clinical features of tuberculosis make the diagnosis of the disease more challenging in the former.[18,21] Various factors seem to influence the balance between the risk of LTBI and the progression to active tuberculosis, such factors including age, nutritional status, BCG vaccination, and immune status.[18,22]

Data regarding active surveillance in the era before tuberculosis treatment suggest that most children develop radiological signs after *M. tuberculosis* infection, including 60-80% of children under 2 years of age. However, less than 10% of those cases were reported,

suggesting that *M. tuberculosis* infection was controlled by the host immune response in most cases.[22,23]

Pulmonary infection with *M. tuberculosis* occurs when bacilli successfully reach a terminal airway, resulting in a localized pulmonary inflammatory process called a parenchymal focus (Ghon focus). From this focus, the bacilli disseminate through the local lymphatic system to regional lymph nodes. A Ghon focus is characterized by local tuberculous lymphangitis and the involvement of regional lymph nodes. This combination is known as the primary complex. From the regional lymph nodes, the bacilli enter the systemic circulation directly or via the lymph duct. This occult hematogenous dissemination occurs before an appropriate immune response is able to prevent the development of active tuberculosis. After dissemination, the bacilli can survive within the target organs for long periods. The future course of active tuberculosis depends on the dynamic balance between the host immunity and the pathogen.[24]

In children under 2 years of age, primary tuberculosis infection frequently progresses to severe disease, without significant prior symptoms, usually in the first 12 months after contact with active tuberculosis cases. In children 2-10 years of age, primary infection rarely progresses to severe disease; when that does occur, it is accompanied by significant clinical symptoms. In children over 10 years of age, primary infection usually evolves to adult-type active tuberculosis. Effective early intervention in this age group will reduce the possibility of cavitary disease and transmission of the disease to the community. The disease has been observed to behave the same way in immunocompromised children as in children with immature immunity (those under 2 years of age).[18,24]

The evolution of tuberculosis after pulmonary infection in childhood includes a number of phases[24]:

- Phase 1 begins 3 to 8 weeks after the primary infection. At the end of the initial asymptomatic period, the patient may present hypersensitivity reactions, such as fever, erythema nodosum, a positive response to the tuberculin skin test (TST), and development of the primary complex, which can be seen on a chest X-ray.
- Phase 2 begins 1-3 months after the primary infection, following the occult hematogenous dissemination that occurs during the incubation. This is the period of greatest risk for the development of tuberculous meningitis and miliary tuberculosis in small children, although these manifestations of tuberculosis may occur at any time after hematogenous dissemination.
- Phase 3 begins 3-7 months after the primary infection. During this phase, there can be pleural effusion in children over 5 years of age and bronchial disease in children under 5 years of age.
- Phase 4 lasts from the end of phase 3 until the calcification of the primary complex, which occurs 1-3 years after the primary infection. In phase 4, osteoarticular tuberculosis can occur in children under 5 years of age and adult-type active tuberculosis can develop in adolescents. In general, the risk of disease progression is minimal when calcification occurs. However, adult-type active tuberculosis, a delayed manifestation following the primary infection, develops after the calcification is present.
- Phase 5 begins after the calcification is concluded, more than 3 years after the primary infection. This phase represents the period of late tuberculosis manifestations, including reactivation of pulmonary tuberculosis.

CLINICAL MANIFESTATIONS OF TUBERCULOSIS IN CHILDHOOD

From the clinical perspective, childhood tuberculosis presents nonspecific signs and symptoms that worsen with time, and some children with active PTB can be asymptomatic, in which case active PTB can be clinically mistaken for LTBI.[25] The main symptoms of pediatric tuberculosis include fatigue, loss of appetite, night sweats, weakness, weight loss, and evening fever. When the disease reaches the lungs, the child can present chest pain and cough (productive or nonproductive), which can, in rare cases, be accompanied by hemoptysis. Other signs and symptoms include fever (moderate, persistent for 15 days or more, and often arising in the evening), weight loss, anorexia, hemoptysis, pallor, lymphadenopathy, and hepatosplenomegaly. Persistent cough (productive or not) is the main symptom of the pulmonary form of the disease, which is the most common form of pediatric tuberculosis.[16,26] Erythema nodosum, keratoconjunctivitis, and joint pain can also occur. It is noteworthy that hemoptysis can occur in adolescence but is rare in childhood.[27]

Tuberculosis can affect organs other than the lungs; approximately 20% of tuberculosis cases in children have extrapulmonary manifestations.[26] In such cases, the symptoms vary according to the organs affected and can occur in the lymph nodes, kidneys, bones, and meninges, among other sites. One of the most serious forms of the disease is miliary tuberculosis, resulting from the hematogenous dissemination of *M. tuberculosis*, which increases the risk of meningitis.[16]

In HIV-infected patients, the clinical presentation of tuberculosis is influenced by the degree of immunosuppression and, in general, the diagnostic investigation in patients with tuberculosis/HIV coinfection is similar to that employed for the general population.[28,29] In addition, because of the greater frequency of extrapulmonary and disseminated forms in HIV-infected children, an appropriate diagnostic investigation includes invasive procedures to obtain clinical specimens (such as those of pleural fluid and cerebrospinal fluid) or biopsy samples from solid organs (such as lymph nodes and the pleura).[29]

DIAGNOSING TUBERCULOSIS IN CHILDREN AND ADOLESCENTS

The diagnosis of tuberculosis in childhood continues to be a challenge. The main international consensus statement on childhood tuberculosis, published by the WHO, emphasizes this notion and states that the

clinical, radiological, and epidemiological features are the most indicative of active tuberculosis in childhood. Therefore, the approach to diagnosing tuberculosis in children is based on the following[17]: careful clinical history taking (including the history of contact with tuberculosis cases and of symptoms consistent with the disease); a thorough clinical examination, with special attention to aspects of childhood development; the TST result; chest X-ray findings (when available); bacteriological confirmation whenever possible; specific investigation of the organ involved in suspected cases of pulmonary and extrapulmonary tuberculosis; and HIV testing. The WHO consensus statement also highlights the importance of seeking bacteriological or molecular confirmation with the molecular test for *M. tuberculosis* and for resistance to rifampin (Xpert MTB/RIF) and does not recommend the so-called "therapeutic test"; that is, the attempt to establish a diagnosis by applying the treatment for tuberculosis and awaiting an improvement in the clinical status of the patient.[17]

In children living with HIV/AIDS, tuberculosis should be investigated at all routine clinical visits by inquiring about the existence of the four main symptoms: fever, cough, night sweats, and weight loss. The presence of any of those symptoms is suggestive of active tuberculosis and indicates the need for a more detailed investigation.[30]

Radiological aspects of tuberculosis in children and adolescents

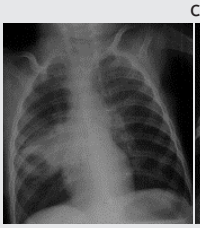
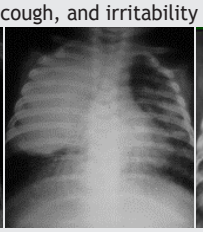
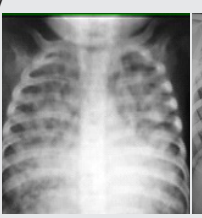
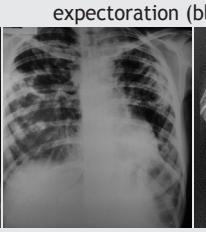
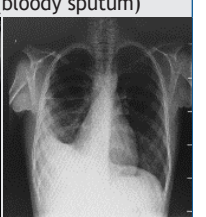
Some of the radiological aspects of tuberculosis in childhood are shown in Chart 1. The radiological aspects most commonly associated with PTB fall into two categories: those observed in patients < 10 years of age; and those observed in patients 10-18 years of age. In children under 10 years of age, there is a predominance of images consistent with primary tuberculosis or the primary complex. In such patients, the primary complex is evolving and the manifestations usually occur within the first 5 years after primary infection. Such manifestations include hilar lymphadenopathy, miliary images (diffuse micronodular or nodular infiltrates, usually bilateral), and characteristics of chronic or slowly evolving pneumonia—also known as expansive pneumonia.[31] In patients 10-18 years of age, the radiological aspect is one of post-primary tuberculosis (i.e., adult type tuberculosis).[31] In such patients, the images are predominantly in the upper third or in the superior segment of the lower lobe of both lungs, often showing cavitations.[31]

Microbiological diagnosis

The confirmation of a diagnosis of tuberculosis by means of bacteriological testing is, in general, difficult to achieve in younger children but viable in those ≥ 10 years of age, who typically develop bacteriological PTB. Most children who develop primary tuberculosis are sputum smear-negative or produce paucibacillary specimens. Children under 8 years of age rarely produce sputum, and the diagnosis of tuberculosis in such children is made without bacteriological confirmation in 80% of cases. For children who cannot expectorate, it is recommended that samples be collected through gastric lavage if possible.[17] However, the use (direct examination and culture) of induced sputum samples in children has proven to be more sensitive than is gastric lavage and is usually well accepted.[32,33]

In practice, the conventional Ziehl-Neelsen method is still used for direct staining for AFB. However, the method has low (10-15%) sensitivity for specimens with a concentration below 5×10^3 bacilli/mL, which explains the negative results in children who produce paucibacillary specimens.[17] The alternative method would be fluorescent light-emitting diode microscopy, which, in most studies, has higher sensitivity and specificity than does Ziehl-Neelsen staining. Likewise, the culture can be carried out on conventional Löwenstein-Jensen medium or, more recently, in Middlebrook 7H9 liquid medium, the latter having the advantages of more rapid *M. tuberculosis* growth and higher sensitivity for paucibacillary specimens (including blood samples). Middlebrook 7H9 has become the culture medium of choice for use in automated methods (Chart 2). Among such methods, the most well-known is the use of the BACTEC Mycobacteria Growth Indicator Tube 960 system, which is a fully automated, nonradiometric method with an average detection time of 7 days.[28]

Chart 1. Most common clinical and radiological aspects of pulmonary tuberculosis in children and adolescents.

Aspect	Pediatric patients				
	< 10 years of age			10-18 years of age	
Signs and symptoms	Persistent fever, weight loss, cough, and irritability			Persistent fever, adynamia, and expectoration (bloody sputum)	
Chest X-ray					
Finding	Right hilar lymphadenopathy	Chronic pneumonia	Miliary pattern	Pulmonary cavitations	Pleural effusion

Molecular diagnosis

The molecular diagnosis of tuberculosis involves genotypic tests based on the amplification of nucleic acids (nucleic acid amplification tests). Such tests include line probe assays and the Xpert MTB/RIF assay. All of these methods offer the great advantage of faster laboratory results and identification of resistance to drugs such as rifampin and isoniazid, as well as high sensitivity and specificity (Chart 2).

The Xpert MTB/RIF assay has been available in several cities in Brazil since 2014. It is a nucleic acid amplification test that employs the technique of real-time polymerase chain reaction on the GeneXpert platform. In Brazil, it is known as the rapid molecular tuberculosis test. The Xpert MTB/RIF assay facilitates the identification of mycobacterial DNA and reduces the risk of cross-reactivity during the amplification of the DNA. Its result can be obtained in the laboratory in approximately 2 h, allowing the identification of *M. tuberculosis* and the detection of rifampin-resistant strains.[34] The incorporation of the molecular diagnosis of tuberculosis has also been recommended for use in children since 2013.[35] The use of the Xpert MTB/RIF assay in pediatric tuberculosis is still limited, because its performance is best in bacteriologically confirmed tuberculosis, which accounts for only a minority of cases in children.[36]

In a retrospective study on the use of the Xpert MTB/RIF assay at primary health care clinics in the city of Rio de Janeiro, the Xpert MTB/RIF assay result was positive (detectable levels of *M. tuberculosis*) in 131 (16%) of 852 cases of suspected tuberculosis in adolescents, rifampin-resistant strains being identified in 3 (2%).[37] A part of the samples obtained from cases detected by the Xpert MTB/RIF assay were submitted to drug susceptibility testing and 17% were found to be resistant to drugs other than rifampin.[37]

Scoring system for tuberculosis diagnosis in childhood

In 2002, the Brazilian National Ministry of Health (NMH) proposed a new scoring system for the diagnosis of intrathoracic tuberculosis (PTB),[15] which has already been validated, in HIV-infected and non-HIV-infected children,[38,39] and tested in other countries,[40,41] showing high accuracy. Recently, a group of authors[42] employed a variety of diagnostic systems, including that proposed by the NMH, to study a cohort of 121 HIV-infected children and adolescents. The NMH system has been found to produce few false-positive results and to be useful as a screening test in such patients (Chart 3). However, the bacteriological diagnosis of active tuberculosis should be carried out whenever possible, because, among other advantages, it allows the identification of *M. tuberculosis* and of the profile of susceptibility to anti-tuberculosis drugs, which is particularly relevant given the increasing number of cases of MDR-TB and XDR-TB.[35]

New diagnostic methods

The recent introduction of a new version of the Xpert MTB/RIF assay, known as the Xpert MTB/RIF Ultra assay, could improve the accuracy of the diagnosis childhood tuberculosis, because its sensitivity is superior to that of the conventional Xpert MTB/RIF assay for paucibacillary samples. The frequency of positive results in respiratory and cerebrospinal fluid samples obtained from children has been found to be greater with the use of the Xpert MTB/RIF Ultra assay than with that of the Xpert MTB/RIF assay.[1]

The string test is a new diagnostic method that has been used for the diagnosis of tuberculosis in children. The patient swallows a capsule containing a thin string, which unravels in the stomach and is coated with gastrointestinal secretion. After some time, the string is removed and the material is sent to the laboratory so it can be processed by bacteriological or molecular methods. The string test resembles conventional gastric lavage but is less invasive. However, there have been few studies of the use of the string test in diagnosing tuberculosis in children. In a study conducted by Nansumba et al.,[43] the results were similar to those obtained from induced sputum.

Chart 2. Bacteriological and molecular methods for the diagnosis of childhood tuberculosis.

Method	Time to results	Sensitivity	Specificity
Microscopy			
Ziehl-Neelsen staining	Same day	32-94%	50-99%
Fluorescent LED	Same day	52-97%	94-100%
Culture			
Liquid media with susceptibility testing	10-21 days	89% (AFB+) 73% (AFB− and culture+)	> 99%
Molecular technique (NAATs)			
Xpert MTB/RIF assay	Same day	98% (AFB+); 67% (AFB−) 95%, RIF-resistant	99% (AFB−) 98%, RIF-resistant
LPA (1 line) [INH and RIF]	1-2 days	98%, RIF; 84%, INH	99%
LPA (2 lines) [Fluo; Injet]	1-2 days	86-87%	99%
LAMP	Same day	76-80%	97-99%

LED: light-emitting diode; NAATs: nucleic acid amplification tests; Xpert MTB/RIF assay: molecular test for *M. tuberculosis* and for resistance to rifampin; RIF: rifampin; INH: isoniazid; LPA: line probe assay; Fluo: fluoroquinolones; Injet: second-line injectable drugs; and LAMP: loop-mediated isothermal amplification. Source: Pai et al.[45]

Chart 3. Diagnosis of pulmonary tuberculosis using the Brazilian National Ministry of Health scoring system in children and adolescents who have tested negative on sputum smear microscopy.[a]

Clinical findings	Chest X-ray findings	History of contact with an adult pulmonary tuberculosis case	TST	Nutritional status
Fever or fatigue, productive cough, weight loss, night sweats for > 2 weeks despite nonspecific antibiotic use	Adenomegaly or miliary pattern; infiltration (with or without cavitations) unaltered for > 2 weeks or worsening despite nonspecific antibiotic use	Close contact for < 2 years	BCG > 2 years prior or no BCG (induration ≥ 5 mm) or BCG < 2 years prior (induration ≥ 10 mm)	Severe malnutrition
Score = 15	Score = 15	Score = 10	Score = 15	Score = 5
Asymptomatic or symptomatic for < 2 weeks	Infiltration (with or without cavitations) for< 2 weeks	No contact or occasional contact	Induration 0-4 mm	Normal
Score = 0	Score = 5			
Respiratory symptoms improved spontaneously or with nonspecific antibiotic use	Normal findings	Score = 0	Score = 0	Score = 0
Score = −10	Score = −5			

TST: tuberculin skin test. [a]Diagnostic interpretation of the chart: ≥ 40 points: highly likely; ≥ 30 and ≤ 39 points: possible; and ≤ 29 points: unlikely. Source: Brasil. Ministério da Saúde.[28]

TREATMENT OF ACTIVE TUBERCULOSIS IN CHILDREN AND ADOLESCENTS

The treatment strategy in Brazil follows what has been proposed by the WHO, separating children under 10 years of age from adolescents and adults. The doses of isoniazid and rifampin have been adjusted according to the WHO standards.[17] The basic treatment regimens for childhood tuberculosis and tuberculous meningitis are detailed in Chart 4 and Chart 5, respectively.

The treatment of MDR-TB (infection with an *M. tuberculosis* strain resistant to at least rifampin and isoniazid) in childhood is still based on the regimens recommended for adults. There has been recent progress toward reducing treatment time in special situations that are relevant to children, mainly due to the recent introduction of the diarylquinoline bedaquiline in such treatment regimens. Therefore, regimens of only 9-12 months can be prescribed in patients who have not previously been treated for MDR-TB.[44] The long-duration regimens in patients with MDR-TB can involve treatment for 20 months or more, according to the particularities of each case. The factors to be considered in choosing between a short and a long treatment regimen for MDR-TB in childhood can be seen in Chart 6.

In special situations, isoniazid and ethambutol can strengthen the treatment regimen for MDR-TB.[35,45] Another drug that is in the process of being incorporated into treatment regimens for children with MDR-TB is delamanid, which has been shown to be effective in studies of tolerance and pharmacokinetics, although such studies have not included patients with HIV infection, heart disease, severe malnutrition, or other comorbidities. The WHO recommends the use of delamanid in the treatment regimen for MDR-TB in children who are not eligible for the previously mentioned short regimen, especially taking into account that there is no safe position regarding the interaction of bedaquiline and delamanid in the same patient.[46] It has been proposed that the administration of delamanid in childhood constitutes compassionate use.[47,48] However, systematic reviews of bedaquiline and delamanid use in children recommend caution and accurate monitoring of the Q_T interval corrected with Fridericia's formula.[49-51] Studies of those drugs are scarce, which limits their current usage.[52]

In the evaluation of tuberculosis/HIV coinfection in children, it is recommended that all individuals diagnosed with HIV/AIDS and active tuberculosis should start combined antiretroviral therapy (ART), regardless of the clinical form of the tuberculosis and the CD4+ T lymphocyte count.[28,29] It should be borne in mind that the atypical forms of the disease occur in patients with a higher degree of immunodeficiency caused by HIV infection.[28,53]

During the treatment of tuberculosis/HIV coinfection, when the ART regimen is chosen, it should be taken into consideration that rifampin is a potent inducer of cytochrome P450 and glycoprotein P, which significantly reduces the plasma concentrations of protease inhibitors and non-nucleoside reverse transcriptase inhibitors, because those drugs use the same metabolic pathway.[28]

Since 2015, formulations of anti-tuberculosis drugs in fixed-dose combinations, presented as dissolvable tablets with a pleasant taste, have been available in the following doses: rifampin (75 mg), isoniazid (50

Chart 4. Basic regimen for the treatment of tuberculosis in children under 10 years of age.

Treatment phase	Drugs	Daily dosage, by patient weight						
		≤ 20 kg	21-25 kg	26-30 kg	31-35 kg	36-40 kg	41-45 kg	≥ 45 kg
		mg/kg	mg	mg	mg	mg	mg	mg
2RHZ	Rifampin	15 (10-20)	300	450	500	600	600	600
	Isoniazid	10 (7-15)	200	300	300	300	300	300
	Pyrazinamide	35 (30-40)	750	1000	1000	1500	1500	2000
4RH	Rifampin	15 (10-20)	300	450	500	600	600	600
	Isoniazid	10 (7-15)	200	300	300	300	300	300

Source: World Health Organization.[17]

Chart 5. Basic regimen for the treatment of tuberculous meningitis in children.

Treatment phase	Drugs[a]	Daily dosage, by patient weight						
		≤ 20 kg	21-25 kg	26-30 kg	31-35 kg	36-40 kg	41-45 kg	≥ 45 kg
		mg/kg	mg	mg	mg	mg	mg	mg
2RHZ	Rifampin	15 (10-20)	300	450	500	600	600	600
	Isoniazid	10 (7-15)	200	300	300	300	300	300
	Pyrazinamide	35 (30-40)	750	1000	1000	1500	1500	2000
10RH	Rifampin	15 (10-20)	300	450	500	600	600	600
	Isoniazid	10 (7-15)	200	300	300	300	300	300

Source: World Health Organization.[17] [a]During the treatment of tuberculous meningitis, a corticosteroid can be added to the anti-tuberculosis regimen: oral prednisone (1-2 mg/kg daily) for four weeks or, in severe cases, intravenous dexamethasone (0.3-0.4 mg/kg daily) for 4-8 weeks, with gradual dose reductions over the subsequent 4 weeks.

Chart 6. Factors to consider when choosing the treatment regimen for children with multidrug-resistant tuberculosis.

- Confirmed susceptibility to or presumed efficacy of all drugs of the short MDR-TB regimen (isoniazid resistance excepted)
- No exposure to the second-line MDR-TB regimen for > 1 month
- No intolerance to any drug in the short non-toxic MDR-TB regimen (i.e., drug interactions)
- Pregnancy excluded
- Pulmonary disease only
- All drugs in the short MDR-TB regimen are available for the program

↓ YES ↓ → Short MDR-TB regimen

Regimen failure, drug intolerance, return after interruption for > 2 months, emergence of an exclusion criterion →

↓ NO ↓ → Longer (individualized) MDR-TB regimen

MDR-TB: multidrug-resistant tuberculosis. Source: Grzemska M.[9]

mg), and pyrazinamide (150 mg) for the intensive phase; and rifampin (75 mg) and isoniazid (75 mg) for the maintenance phase. Although those formulations are not yet available in Brazil, there are ongoing negotiations to acquire them. There are as yet no second-line drugs available in formulations suitable for children. Therefore, the treatment of MDR-TB still presents obstacles related to the administration of many drugs that need to be adapted to administration in pediatric patients, which clearly has a negative impact on adherence.[54,55]

TUBERCULOSIS PREVENTION IN CHILDREN

The health interventions currently available for tuberculosis prevention which relate specifically to children are LTBI treatment and BCG vaccination. LTBI is defined as a state of persistent immune response to exposure to *M. tuberculosis* without clinical or radiological evidence of active tuberculosis.[56] Adults and children who are in contact with smear-positive PTB patients are at a higher risk of LTBI and of progression from LTBI to active disease, as well as a higher incidence of active tuberculosis.[57-60] The pharmacological treatment of LTBI is the main intervention capable of preventing the progression to active tuberculosis in such individuals.[2]

Children, in particular those under 5 years of age, represent a group for which there is clear evidence of the benefits of testing for and treating LTBI.[58-60] The WHO,[59] the International Union against Tuberculosis and Lung Disease,[19] and the International Standards for Tuberculosis Care,[61] as well as the main North-American and European guidelines,[62-65] are unanimous in recommending that, after active tuberculosis has been excluded, LTBI be treated in two high-risk groups: children under 5 years of age and people living with HIV who have been exposed to cases of bacteriologically

confirmed PTB. Screening children under 5 years of age for active tuberculosis and LTBI is a strategy recommended by the WHO, even in countries with limited resources.[57,59]

The Brazilian National Tuberculosis Program guidelines recommend that the investigation and, if necessary, the treatment of LTBI in children under 5 years of age who have been in contact with smear-positive PTB cases be prioritized.[28] However, only 44.9% of such contacts were screened in 2015 in the country as a whole; in the states of Amapá and Rio de Janeiro, that proportion was only 22.3% and 22.1%, respectively, in that same year.[3]

In 2016, there were, worldwide, approximately 1.3 million children under 5 years of age who were close contacts of bacteriologically confirmed PTB cases and were therefore eligible for preventive tuberculosis treatment. Although the number of children in this age group who reportedly started the treatment for LTBI increased by 85% between 2015 and 2016, it still represents only 13% of the children who are eligible to receive treatment.[1]

Administration of the treatment for LTBI in children under 5 years of age who are contacts of smear-positive PTB cases (some guidelines use the term "cases of contagious tuberculosis", also including cases of laryngeal tuberculosis) is recommended whether or not there has been confirmation of LTBI.[56,57,61] As in adults, the diagnosis of LTBI in children is based on the results of a TST performed by the Mantoux method. The interpretation of those results (skin induration measured in millimeters) varies according to the degree of exposure to the index case and to the BCG immunization status. In Brazil, children and adolescents who are household contacts of PTB cases and have not been vaccinated with BCG or were vaccinated more than 2 years prior are considered positive if their response to a TST is a skin induration of at least 5 mm. In the case of those vaccinated with BCG less than 2 years prior, the cut-off induration for positivity is 10 mm. Contacts initially showing negative TST results should repeat the test after 8 weeks.[28]

Interferon-gamma release assays (IGRAs) have lower sensitivity in children under 2 years of age and in those who are immunosuppressed; IGRAs are not typically recommended for use in this age group.[17,65,66] The frequency of indeterminate test results among such children is apparently higher with the QuantiFERON-TB Gold In-Tube test than with the T-SPOT.TB test. For older children, the sensitivity and specificity of the QuantiFERON-TB Gold In-Tube test and the T-SPOT.TB test are comparable to those reported for their use in adults. However, in comparison with TSTs, IGRAs are more expensive and require laboratory support that is more sophisticated, therefore not being indicated as a substitute for TST in regions where resources are limited.[17,56]

The recommended treatment regimens for LTBI are as follows[56,62]: isoniazid daily for 6 months or 9 months (the 9-month regimen is the only one that the U.S. Centers for Disease Control and Prevention recommend for use in children); isoniazid plus rifampin daily for 3-4 months; rifampin daily for 3-4 months; and isoniazid plus rifapentine weekly for 3 months (not recommended for children under 2 years of age or for HIV-infected patients on ART).

The effectiveness of treating LTBI with isoniazid for 6-12 months (ideally, for 9 months) is estimated to be 60-90%, with no significant differences in the level of protection among treatments of different durations.[67] A recent review showed that prophylaxis with isoniazid given to HIV-infected children in Africa reduces the risk of active tuberculosis and death among those who are not on ART, although there was no clearly observed benefit for the children who are on ART.[68] The use of the 6-month regimen of isoniazid (5-10 mg/kg daily, up to a maximum of 300 mg/day) is the strategy recommended by the Brazilian National Tuberculosis Program, and the regimen is generally well tolerated by children and adolescents.[28] For adults and children who are contacts of MDR-TB cases, there are as yet no regimens for preventive treatment based on efficacy studies, although the execution of such studies is considered a priority by the scientific community. The combination of at least two drugs (at least one of which should be a bactericide) is the regimen recommended by experts.[35,69]

One of the priority indicators of the End TB Strategy is the preventive treatment of ≥ 90% of HIV-infected individuals and children who are contacts of PTB cases.[4] However, to achieve that objective, it will be necessary to increase the capacity of programs to investigate contacts and to offer preventive therapy. Several barriers to the preventive treatment in children have been identified, such as the inability to exclude active tuberculosis, the fear of creating resistance to tuberculosis drugs, the poor adherence to long-duration treatment regimens, the low socioeconomic level of some families, and poor adherence to active tuberculosis treatment by index cases.[14,70] Unless those barriers can be overcome, the indicators concerning the investigation of contacts and the completion of preventive tuberculosis treatment with isoniazid in children will be far from what is expected.

For more than 100 years, the BCG vaccine has been available for the primary prevention of tuberculosis in children. Although the vaccine prevents 60-90% of cases of the severe forms of active tuberculosis in children (disseminated forms and tuberculosis meningitis), it is not efficacious in the prevention of the disease in adults.[17] In Brazil, there is a high level of BCG immunization coverage.[3,28] However, that has not had a significant impact on the number of cases of PTB or the less severe forms of extrapulmonary tuberculosis among children infected by *M. tuberculosis* after vaccination. The slow decline in the incidence of tuberculosis observed worldwide in recent decades underscores the need for a more effective vaccine against tuberculosis, one that would provide protection

against all forms of tuberculosis in different age groups. In 2017, there were 12 new tuberculosis vaccines being tested in phase I, II, or III trials.[1]

FINAL COMMENTS

Children represent the most fragile link among the complex mechanisms currently involved in the control of tuberculosis. In order to achieve the ambitious goals outlined in the End TB Strategy, concerted efforts are required from the various sectors of society. Priority should be given to measures that address the peculiarities of tuberculosis in childhood: ensuring the early identification (through contact screening) and treatment of active tuberculosis and LTBI in children; using methods that are more sensitive and less invasive for the diagnosis of extrapulmonary tuberculosis and of tuberculosis in patients who produce paucibacillary samples; making child-friendly anti-tuberculosis drugs more widely available; developing tuberculosis vaccines that are more effective; and formulating new drugs for resistant forms of tuberculosis that have low toxicity in children. Adequate financial resources and political will are essential if these goals are to be met and tuberculosis is finally to be removed from the list of the leading causes of death among children worldwide.

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