Updated diagnosis and treatment of childhood tuberculosis

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Background: **Childhood tuberculosis (TB) accounts for a significant proportion of the global tuberculosis disease burden. However, current and previous efforts to develop better diagnostic, therapeutic, and preventive interventions have focused on TB in adults, and childhood TB has been relatively neglected. The purpose of this review is to provide an update on the diagnostic and therapeutic recommendations for childhood TB with an emphasis on intrathoracic disease.**

Data sources: **The literature from a range of sources was reviewed and synthesized to provide an overview of the contemporary approaches for the diagnosis and treatment of childhood TB.**

Results: **This review summarizes the clinical, radiological, bacteriological, and immunological approaches to diagnose TB infection and disease in children. In addition, we summarize the updated guidelines for the treatment of TB in children.**

Conclusions: **The development of better diagnostic and therapeutic methods for childhood TB remains a significant challenge. As the strategies for diagnosis and treatment of childhood TB continue to improve and the knowledge base increases, the implementation of these strategies will be crucial.**

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Introduction

Childhood tuberculosis (TB) accounts for approximately 15%-40% of all TB cases.[1-5] High rates of transmission are sustained in TB-endemic areas due to high case density and prolonged diagnostic delay.[6] Because childhood TB reflects ongoing transmission, children are most often affected in areas where the adult epidemic is poorly controlled.[7] In addition, childhood TB remains neglected for various reasons, including the difficulty in diagnosing pulmonary TB, the lack of scientific studies on childhood TB, the largely unknown outcomes of children with TB, and the belief that childhood TB is not an important factor in TB control.[8,9] In recent years, there have been several important developments in the diagnosis and treatment of childhood TB infection and disease. This article provides a brief overview of current controversies and recent advances in the care of children with TB with an emphasis on intrathoracic disease.

Data collection

We initially collected all of the articles that were published from January 2002 to June 2012, which described children who were affected by TB. These articles were obtained by searching MEDLINE using the key words "childhood tuberculosis" and "diagnosis of tuberculosis or management of tuberculosis". Articles that were not published in the English language, those without an abstract (which were assumed not to be original), and opinion articles were excluded from the review. After selecting the articles, the relevant information was extracted and classified according to TB diagnosis, TB management, the country of the first author, the year of the publication, and the study design.

Literature searching was performed in May 2012 and June 2012. Using the search terms previously described, 163 articles were retrieved from MEDLINE. Finally, 109 of them were considered to be relevant. The first authors of these articles were primarily from India, South Africa, the United Kingdom, the United States, Germany, and Australia. About 35% of the articles, which belonged to original category were from India. After analyzing the abstracts of the articles, we found that 85% of the studies were retrospective, 10%

were prospective, and 5% were other designs.

Diagnosis of TB infection

Tuberculin skin test

A positive tuberculin skin test (TST) reaction has been used as a hallmark of infection with *M. tuberculosis*, which occurs within 3 to 6 weeks of infection but occasionally up to 3 months after infection and remains positive for life time even after treatment.[10-12] The test is read 48-72 hours after injection. The Mantoux test is the standard tuberculin test that is recommended for use, which involves an intradermal injection of 2 tuberculin unit purified protein derivative (TU PPD).[13] The evoked reaction is dependent on the amount of antigen administered; however, there is no linear relationship between the reaction and an increasing strength of the antigen dose.[14] A prior Bacillus Calmette-Guérin (BCG) vaccine at birth may influence the PPD reaction under 3 years of age, but does not interfere with PPD reaction above 3 years of age.[15,16] When the patient returns for a TST reading after 72 hours but before the 7th day post-injection, a positive test is still valid.[17] A repeat test may be needed if there is no induration and the wheals appear after the stipulated time for reading. A repeat tuberculin test, when required, should preferably be performed on the opposite arm.[17] In the United Kingdom,[18] a TST is considered positive when the induration is 5 mm or more in diameter in patients without prior BCG vaccination. In contrast, the World Health Organization (WHO) guidelines suggest that a TST is positive when the induration is more than 10 mm in diameter in patients without prior BCG vaccination and more than 15 mm in diameter in patients with prior BCG vaccination.[19] The guidelines in Taiwan use a risk categorization that is based on epidemiological and clinical factors (Table 1).[20]

Tuberculin skin tests are prone to both false-negative and false-positive results. In otherwise immunocompetent children with culture-documented TB, 10%-15% of these children do not initially exhibit TST reactivity.[21] Host factors, such as young age, poor nutrition, immunosuppression, viral infections, recent TB infection, and disseminated TB disease, can further decrease TST reactivity.[22,23] Most of consensus documents concerning TST interpretation agree that malnutrition can cause a TST false negative result;[22] however, some studies[23,24] conclude that only some co-morbidities can modify TST, without specific nutritional status. In addition, false-positive TST results may occur after BCG vaccination and exposure to environmental non-tuberculous mycobacteria.[25] In many children and adults who receive BCG vaccination, skin reaction can be boosted by antigenic stimulation during serial testing with TST.[26]

Interferon-gamma release assays

Because of the limitations of TST, new diagnostic tests have been developed. Interferon-gamma release assays (IGRAs) are blood-based assays and have recently become available. These T-cell-based assays rely on the stimulation of host blood cells with *M. tuberculosis*-specific antigens (early secretory antigenic target-6, the culture filtrate protein 10, and QuantiFERON-TB Gold TB 7.7), and are used to measure the production of interferon-γ. Two available commercial assays, the T-Spot TB assay (Oxford Immunotec, Inc., Abingdon, UK) and the QuantiFERON-TB Gold assay (Cellestis, Ltd., Carnegie, Victoria, Australia) are compared, with TST for the detection of both active disease and latent tuberculosis infection.[27] Overall, the results indicate that IGRAs have a modest predictive value, which is similar to that of TST. In the settings with a low TB incidence, the IGRAs demonstrated a higher

Table 1. Interpretation of positive Mantoux tests in children

British Thoracic Society[18]	World Health Organization[19]	Taiwan Centers for Disease Control[20]
10TU PPD per 0.1 mL	5TU PPD-S per 0.1 mL (alternatively 2 TU PPD RT23)	2TU PPD RT23
5-14 mm if not BCG vaccinated	≥ 5 mm if one of the following: HIV positive children Severely malnourished children (clinical evidence)	≥5 mm if one of the following: Cancer Organ transplant Immunosuppression
>15 mm if BCG vaccinated	≥10 mm for all other children whether BCG vaccinated or not	≥10 mm and if one of the following: Children aged >6 years and BCG vaccinated >6 years or without BCG vaccinated or with one of following risk factors: close contact with active TB patients; having family history of TB; having chronic diseases, such as diabetes Malnutrition Drug abuser >15 mm and if children aged ≤6 years or BCG vaccinated ≤6 years

TU: tuberculin unit; PPD: purified protein derivate; BCG: Bacille Calmette-Guérin; HIV: human immunodeficiency virus; TB: tuberculosis.

specificity (100% and 98% for the QuantiFERON-TB assay and the T-Spot assay, respectively) than TST (58%) in children with TB.[28] A study of children with TB disease indicated lower sensitivities of the T-spot TB assay (58%) and the QuantiFERON TB assay (80%) compared with the TST (83%).[29] A study[30] indicated a higher sensitivity of 100% and a specificity of 93% for TST at a cut-off point of >5 mm in children without BCG vaccination. In BCG-vaccinated children, the TST cut-off point of >10 mm had a poor specificity (86%), and the cut-off point of >15 mm results in a reduced sensitivity of 60%. Another significant problem with IGRAs has been the risk of indeterminate tests, particularly in younger children and immunocompromized individuals.[31] The rates of indeterminate tests are higher for the QuantiFERON-TB Gold assay than for the Enzyme-linked Immunosorbent Assay in immunosuppressed individuals.[32,33]

T-cell assays are more specific than TST, but these tests currently cannot distinguish between active disease and latent tuberculosis infection.[27] Therefore, the interpretation of the test results is dependent on the clinical context. Few studies[34,35] have presented pediatric T-cell assay data, but none of these studies assessed age-related performance. Therefore, the performance of T-cell assays in very young children and in immunocompromised individuals, such as patients with human immunodeficiency virus (HIV), is not well-defined. The costs and technical demands of IGRAs will most likely limit the wide use of these assays in resource-poor settings where better tests are in high demand.

Another immune-based approach is the measurement of the immune response to the transdermal application of *M. tuberculosis* MPB-64 antigen. In pilot studies, the MPB-64 skin patch test can successfully distinguish between active TB and latent tuberculosis infection (LTBI) (a sensitivity of 88%-98% and a specificity of 100%).[36]

The search for novel biomarkers in the blood or urine that can reliably distinguish between active and latent tuberculosis in children with or without co-infections remains an important goal.[37-39] Well-defined cohorts of pediatric patients in tuberculosis-endemic and non-endemic settings will be essential for the initial screening and future validation of such potential markers.[40]

Diagnosis of disease

Clinical features

The diversity of the clinical presentation and the non-specific nature of the symptoms of TB complicates the diagnosis. Low-grade or intermittent fever may be observed but not frequently.[9] A cough of recent onset that lasts longer than 2 weeks should be suspicious of TB.[41] Therapeutic trials with anti-TB drugs are not recommended; however, efforts should be made to confirm the diagnosis. The clinical signs are often subtle, and no diagnostic scoring has been adequately validated.[42]

Chest radiograph

A chest radiograph localizes the site of pathology; however, this test does not confirm disease etiology.[43] The chest radiograph of a child with bronchiectasis or an interstitial lung disease may present non-resolving shadows with persistent symptoms. Ultrasonography of the chest is helpful to assess pleural fluid collection, but decubitus chest X-ray film may reveal similar information. Computed tomography (CT) has been useful in identifying the signs of early pulmonary disease, such as cavitation and intrathoracic hilar lymphadenopathy.[44] There is no evidence that these adenopathies indicate active disease or that these children require different treatments. Consequently, until demonstrated otherwise, pulmonary CT scanning and changes in chemoprophylaxis are not justified in children with tuberculosis infection.[45] Additionally, central nervous system disease, such as TB meningitis or a tuberculoma, may be identified by CT. High-resolution CT offers excellent anatomical visualization.[46] However, because of the high cost of CT and the high level of radiation to which the patient is exposed,[43] compared with other forms of imaging, CT should be reserved for complicated cases. Both CT and magnetic resonance imaging (MRI) are particularly helpful in visualizing the intracranial effect of the disease; however, MRI is more sensitive in the detection of brain stem lesions and early perfusion defects in patients with tuberculous meningitis, and MRI allows for a superior evaluation of the spine and soft tissue.[47]

Bacteriological diagnosis/confirmation

A confirmation of acid-fast bacilli (AFB) from any type of body fluid or tissue is the gold standard for the diagnosis of tuberculosis. Such proof is often lacking in childhood tuberculosis cases because of the difficulty in the collection of sputum and because of paucibacillary primary disease in children. However, positive AFB test yield in advanced cases may be as high as in adults. The reported bacteriological positivity is as high as 33% even in early primary disease states, such as hilar adenopathy.[43,44] Therefore, efforts must be made to confirm a diagnosis with bacteriological testing in every case of suspected tuberculosis. The examination of

sputum-induced or spontaneous gastric aspirates (GAs), bronchial washings, and any other appropriate body fluid may be undertaken. In addition, bronchoalveolar lavage (BAL) can be performed when available. To date, the sensitivity and specificity of GA examination and BAL are similar; however, GA examination is easier to perform.[48] A gastric aspirate collected in the early morning is the preferred specimen for most young children with suspected TB. The aspirate is preferable for detecting AFB and isolating *M. tuberculosis*.[49] Clinicians should collect at least three samples, regardless of the method that is selected.

Ziehl-Neelsen and fluorochrome stains, such as auramine and rhodamine stains, have been the standard and rapid diagnostic tools for TB.[50,51] A Ziehl-Neelsen stain can reveal AFB only if the sample contains more than 10 000 bacilli per mL. Recent advances in light-emitting diode (LED) technology have widened the application of fluorescent microscopy.[52]

Mycobacterial culture of respiratory samples is a useful method for diagnosis in children with suspected pulmonary TB. Different culture methods, such as Löwenstein-Jensen (LJ) medium (solid medium), radiometric methods (BATEC 12B liquid medium), and non-radiometric methods (BATEC MGIT 960 system) (Becton Dickinson Diagnostic Instrument System, Towson, MD, USA), can be used to confirm a diagnosis in the paucibacillary state.[53] Newer methods offer faster results and may be used when available.

New culture-based methods, such as TK medium (SALUBRIS, Woburn, MA, USA), use multiple dye indicators, which allow for the early detection of mycobacterial growth using the naked eye.[54] Colorimetric systems reduce turnaround times, but the accuracy and robustness of these methods in field conditions have not been reported. The drug susceptibility assay uses an inverted light microscope to rapidly detect mycobacterial growth in liquid growth media.[52] This assay has demonstrated excellent performance in field conditions.

Bacteriophage-based assays use bacteriophage viruses to infect and detect the presence of viable *M. tuberculosis* isolates in clinical samples and culture isolates. The following two main approaches have been developed: (1) the use of phage amplification to detect the presence of mycobacteria and (2) the detection of the light that is produced by luciferase reporter phages after infection of live *M. tuberculosis*. When the assays detect *M. tuberculosis* in drug-free samples but fail to detect *M. tuberculosis* in drug-containing samples, the strains are classified as drug susceptible. Phage assays have a turnaround time of 2-3 days, and these assays require a similar laboratory infrastructure to that required for standard cultures. There is no information on the utility of these tests in the diagnosis of childhood TB.[29]

The use of a gas sensor array electronic nose (E-nose) to detect different *Mycobacterium* species in the headspaces of cultures and sputum samples is another innovative approach that is currently in development. The array uses 14 sensors to profile an odor by assessing the change in the electrical properties of each sensor when the array is exposed to a specific odor mixture. In a recent study that analyzed sputum samples from adult TB and non-TB patients, the E-nose had a sensitivity of 68% and a specificity of 69%.[55] Additional research is required to improve the sensitivity and specificity of this test and determine the potential usefulness of this test in the diagnosis of childhood TB.

Molecular diagnostics

Diagnostic methods for *M. tuberculosis* have recently improved, and nucleic acid-based amplification techniques (NAATs) now allow for rapid and sensitive detection in clinical settings.[56,57] Currently, several assays are commercially available for the detection of *M. tuberculosis* bacteria. NAATs that use polymerase chain reaction (PCR) cannot differentiate between living and dead bacilli; therefore, these tests continue to produce positive results even after successful treatment. PCR tests are positive in 95%-100% of culture-positive cases but in only 50%-60% of culture-negative cases.[58]

Real-time PCR has become increasingly available for clinical use, and this test has the advantage of lower cross-contamination and the ability to identify rifampicin resistance. The *rpoB* gene of *M. tuberculosis* accounts for more than 95% of rifampicin resistance. Because rifampicin resistance is usually accompanied by isoniazid resistance, this test is used as a marker for multi-drug resistant TB.[29]

Line probe assays (LPAs) are NAATs that simultaneously detect infection with *M. tuberculosis* and amplify regions of drug resistance. These assays use strip technology in which amplified DNA is applied to strips that contain probes specific for *M. tuberculosis*, isoniazid, and rifampicin resistance. The WHO has endorsed LPAs for culture and smear-positive clinical specimens as part of a larger commitment to target and implement new technology in countries with a high burden of TB.[59]

In addition, NAATs have been used for the rapid detection of rifampicin resistance directly from sputum specimens. The Xpert mycobacterium tuberculosis/resistance to rifampicin is a cartridge-based, automated diagnostic test that is rapid and simple to use. This test correctly identified 98% of bacteria that were resistant to rifampicin in a large study in adults.[29]

Table 2. World Health Organization recommendations for tuberculosis treatment regimens for children[60,62]

Disease	Setting	Anti-TB drug regimens	
		Intensive phase	Continuation phase
Extensive pulmonary	Any	2HRZE	4HR
Mild-to-moderate pulmonary	High HIV or high isoniazid resistance	2HRZE	4HR
Mild-to-moderate pulmonary	Low HIV or low isoniazid resistance	2HRZ	4HR
Lymphadenitis	High HIV or high isoniazid resistance	2HRZE	4HR
Lymphadenitis	Low HIV or low isoniazid resistance	2HRZ	4HR
Meningitis	Any	2HRZE	4HR
Osteoarticular	Any	2HRZE	4HR

H: isoniazid; R: rifampicin; Z: pyrazinamide; E: ethambutol; TB: tuberculosis; HIV: human immunodeficiency virus; 2HRZ 4HR: a two-month intensive phase of daily isoniazid, rifampicin, and pyrazinamide, followed by a four-month continuation phase of daily isoniazid and rifampicin.

Table 3. Treatment regimens for children recommended by Centers for Disease Control, Taiwan, China[20]

Category of disease	Anti-TB drug regimens	
	Intensive phase	Continuation phase
PTB, mild EPTB	2HRZ*	4HR
Severe EPTB	2HRZ*	7-10HR
TB meningitis	2HRZA or 2HRZP	7-10HR
MDR	Individualized regimens	
HIV infection	2HRZ	7-10HR

TB: tuberculosis; PTB: pulmonary tuberculosis; EPTB: extra-pulmonary tuberculosis; H: isoniazid; R: rifampicin; Z: pyrazinamide; A: aminoglycoside; P: prothionamide; 2HRZ 4HR: a two month intensive phase of daily isoniazid, rifampicin, and pyrazinamide followed by four-month continuation phase of daily isoniazid and rifampicin; HIV: human immunodeficiency virus. *: Three drugs (isoniazid, rifampicin, and pyrazinamide) initial regimen are only recommended in countries where primary resistance to isoniazid under 4%.

Management of tuberculosis

The principles of TB treatment for adults and children are the same. Combination regimens that are used to treat active disease aim to eliminate actively replicating, dormant, and near-dormant mycobacteria. The regimens consist of a combination of drugs with minimum toxicity that has different actions, which prevent the emergence of drug-resistant organisms.[60]

TB treatment consists of two phases: an intensive phase with a combination of bactericidal drugs to kill the rapidly growing bacilli and a continuation phase with fewer drugs to eradicate the slower-growing persistent bacilli.[60] The adjunctive use of steroids in TB meningitis treatment has reduced mortality rate and severe disability.[61]

Fixed-dose combination tablets have increased adherence to treatment regimens; however, the marked differences in the absorption, distribution, and excretion of pharmacological agents in children of various ages may require dose adjustments.[62] Tables 2 and 3 list the regimens by disease category that are currently recommended by the WHO and the Taiwan Centers for Disease Control (CDC).[20,60,62] Pharmacokinetic studies have been performed in children and have indicated that age is a determinant of the serum levels of all first-line anti-TB drugs and that infants and young children have lower peak serum levels than older children or adults.[20,60,63,64] The revised recommended dosages are listed in Table 4.

Table 4. First line-anti-TB drugs for children currently recommended by WHO[60,62] and Centers for Disease Control (CDC), Taiwan, China[20]

Drug	Daily dosage (dose range) in mg/kg	
	Recommended by WHO	Recommended by Taiwan CDC, China
First-line oral agents		
Isoniazid	10-15	10-15
Rifampicin	10-20	10-15
Pyrazinamide	30-40	15-20
Ethambutol	15-25	15-20
Injectable agents		
Streptomycin	15-20	20-40
Amikacin	15-22.5	15-30
Kanamycin	15-30	15-30
Capreomycin	15-30	
Second-line oral bacteriostatics		
Prothionamide	15-20	15-20
Ethionamide	15-20	10-15
Cycloserine	15-20	10-20
Para-aminosalicylic acid	150	150-600
Fluoroquinolons		
Moxifloxacin	7.5-10	7.5-10
Ciprofloxacin	20 twice daily	
Levoflaxacin	7.5-10	7.5-10
Ofloxacin	15-20	

WHO: World Health Organization.

Drug-resistant tuberculosis

Poor patient compliance to anti-TB therapy is the major contributory factor to TB control program failure and has led to increasing drug resistance.[62] Diagnosing cases who present with symptoms, coupled with effective treatment to ensure that most are cured, has contributed to both developing and developed countries.[65] After the institution of nationwide Directly Observed Treatment Strategy programmes, the annual risk of infection declined in Chile, Cuba and Uruguay.[66] The rates of drug resistance to any TB drug range from 20% to 80% in different geographic regions.[62] Resistance should be suspected when an index case has known resistant TB, when the child demonstrates initial improvement on anti-TB treatment and then deteriorates, or when there is no response to the initial treatment. Sometimes, the

deterioration of the child condition after initial anti-TB treatment could also be due to the paradoxical effect of TB therapy, not always due to drug resistance. Acquired resistance is well-described in adults who are co-infected with HIV and who were previously treated for TB, which possibly results from malabsorption of the anti-TB medications.[67,68] In addition, the presence of acquired resistance in the pediatric population has been reported, and children with HIV/TB co-infections should be closely monitored.[68]

The global epidemiology of drug resistance has worsen over the past 40 years, particularly with the emergence and increased recognition of multi-drug resistant (MDR) and extensively drug resistant (XDR) tuberculosis.[69] The disease burden of drug resistant tuberculosis can be reduced by treating contacts at high risk of TB infection and of progressing from TB infection to disease.[70] Treatment for MDR TB disease is expensive and is associated with poor prognosis and high risk of toxic effects.[71] Principles for management of drug-resistant TB in children have been summarized elsewhere.[70] Excellent outcomes have been reported.[72,73] Current guidelines recommend using at least four drugs in treatment-naïve patients, including an injectable agent and a fluoroquinolone, during an initial phase for at least 6 months.[74,75] The initial phase should be followed by the use of at least three of the most active and best tolerated drugs during a 12- to 18-month continuation phase. Standardized regimens have been developed for settings where drug susceptibility testing is not available.[76] Six classes of second-line drugs are available;[76] however, research regarding the use of these drugs in children is limited, and multicenter pediatric trials are needed.[74] The rates of MDR strains (resistant to both isoniazid and rifampicin), including XDR strains (also resistant to fluoroquinolones and at least one second-line injectable agent, such as amikacin, kanamycin, and/or capreomycin), are increasing around the world.[67]

Latent TB infection

The duration of LTBI treatment varies by region. In the United States, 9 months of isoniazid is the recommended regimen for treating drug-susceptible LTBI in children according to the guidelines of the American Thoracic Society and the CDC.[77] In contrast, both the WHO and the National Institute for Health and clinical Excellence endorse a 6-month isoniazid regimen for children.[78] In the US Guidelines, the 6-month regimen is an acceptable alternative only for non-HIV-infected adults. Six months of therapy provides a substantial degree of protection; but data suggest that longer regimens are superior.[79] One study showed that a 3-month regimen of preventive therapy with isoniazid and rifampin was similar to efficacy to a 9-month regimen of isoniazid alone for treatment of LTBI in children.[80]

Conclusion

Advances in TB diagnostic tool development over the last decade have produced promising methods to overcome the main barriers in TB care and control. In the future, new tools in the pipeline need to be rapidly assessed and deployed if these tools are found to be effective. The use of diagnostic tools without appropriate treatment constitutes an untenable situation. Therefore, as we capitalize on technological advancements, the commitment to treatment should increase. Closing the gaps between our knowledge of diagnostics, drugs, and the delivery of patient care is needed while we wait for the next wave of new technologies.

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References

1 WHO Report. Global tuberculosis control. Epidemiology, strategy, financing. Geneva: World Health Organization, 2009.
2 Newton SM, Brent AJ, Anderson S, Whittaker E, Kampmann B. Paediatric tuberculosis. Lancet Infect Dis 2008;8:498-510.
3 Nelson LJ, Wells CD. Global epidemiology of childhood tuberculosis. Int J Tuberc Lung Dis 2004;8:636-647.
4 Lu TH, Huang RM, Chang TD, Tsao SM, Wu TC. Tuberculosis mortality trends in Taiwan: a resurgence of non-respiratory tuberculosis. Int J Tuberc Lung Dis 2005;9:105-110.
5 Yeh YP, Chang HJ, Yang J, Chang SH, Suo J, Chen TH. Incidence of tuberculosis in mountain areas and surrounding townships: dose-response relationship by geographic analysis. Ann Epidemiol 2005;15:526-532.
6 Marais BJ, Obihara CC, Warren RM, Schaaf HS, Gie RP, Donald PR. The burden of childhood tuberculosis: a public health perspective. Int J Tuberc Lung Dis 2005;9:1305-1313.
7 Marais BJ. Childhood tuberculosis: epidemiology and natural history of disease. Indian J Pediatr 2011;78:321-327.
8 Yu MC, Suo J, Huang C, Bai KJ, Lin TP, Luh KT. Annual risk of tuberculous infection in Taiwan, 1996-1998. J Formos Med Assoc 1999;98:496-499.
9 Marais BJ, Gie RP, Hesseling AC, Schaaf HS, Lombard C, Enarson DA, et al. A refined symptom-based approach to diagnose pulmonary tuberculosis in children. Pediatrics 2006;118:e1350-1359.
10 Hsu KH. Tuberculin reaction in children treated with isoniazid. Am J Dis Child 1983;137:1090-1092.
11 Chan PC, Chang LY, Wu YC, Lu CY, Kuo HS, Lee CY, et al.

Age-specific cut-offs for the tuberculin skin test to detect latent tuberculosis in BCG-vaccinated children. Int J Tuberc Lung Dis 2008;12:1401-1406.
12 Wang PD. Assessment of the need for universal BCG vaccination of children in Taipei. Public Health 2009;123:74-77.
13 Bowerman RJ. Tuberculin skin testing in BCG-vaccinated populations of adults and children at high risk for tuberculosis in Taiwan. Int J Tuberc Lung Dis 2004;8:1228-1233.
14 Chadha VK. Tuberculin test. Indian J Pediatr 2001;68:53-58.
15 Araujo Z, de Waard JH, de Larrea CF, Borges R, Convit J. The effect of Bacille Calmette-Guérin vaccine on tuberculin reactivity in indigenous children from communities with high prevalence of tuberculosis. Vaccine 2008;26:5575-5581.
16 Piñeiro R, Mellado MJ, Cilleruelo MJ, García-Ascaso M, Medina-Claros A, García-Hortelano M. Tuberculin skin test in bacille Calmette-Guérin vaccinated children: How should we interpret the results? Eur J Pediatr 2012;171:1625-1632.
17 Wang L, Turner MO, Elwood RK, Schulzer M, FitzGerald JM. A meta-analysis of the effect of Bacille Calmette Guérin vaccination on tuberculin skin test measurements. Thorax 2002;57:804-809.
18 Joint Tuberculosis Committee of the British Thoracic Society. Chemotherapy and management of tuberculosis in the United Kingdom: recommendation 1998. Thorax 1998;53:536-548.
19 Guidance for national tuberculosis programmes on the management of tuberculosis in children. Chapter 1: introduction and diagnosis of tuberculosis in children. Int J Tuberc Lung Dis 2006;10:1091-1097.
20 Centers for Disease Control. Taiwan Guidelines for TB Diagnosis and Treatment. Centers for Disease Control, Taiwan, 2011.
21 Starke JR, Taylor-Watts KT. Tuberculosis in the pediatric population of Houston, Texas. Pediatrics 1989;84:28-35.
22 Piñeiro R, Cilleruelo MJ, Mellado MJ. Indications and interpretation of tuberculin skin test. Form Act Pediatr Aten Prim 2010;3:114-116.
23 Piñeiro R, Cilleruelo MJ, García-Hortelano M, García-Ascaso M, Medina-Claros A, Mellado MJ. Effect of nutritional status on tuberculin skin testing. Indian J Pediatr 2012; DOI:10.1007/s12098-012-0773-1.
24 Piñeiro-Pérez R, García-Hortelano M, Mellado MJ, García-Ascaso M, Medina-Claros A, Fernández N, et al. Is there interference in the interpretation of the tuberculin skin test in children with intestinal parasitic infestation? Pathog Glob Health 2012;3:172-176.
25 Larsson LO, Bentzon MW, Lind A, Magnusson M, Sandegård G, Skoogh BE, et al. Sensitivity to sensitins and tuberculin in Swedish children. Part 5: A study of school children in an inland rural area. Tuber Lung Dis 1993;74:371-376.
26 Sepulveda RL, Burr C, Ferrer X, Sorensen RU. Booster effect of tuberculin testing in healthy 6-year-old school children vaccinated with Bacillus Calmette-Guérin at birth in Santiago, Chile. Pediatr Infect Dis J 1988;7:578-581.
27 Arend SM, Thijsen SF, Leyten EM, Bouwman JJ, Franken WP, Koster BF, et al. Comparison of two interferon-gamma assays and tuberculin skin test for tracing tuberculosis contacts. Am J Respir Crit Care Med 2007;175:618-627.
28 Detjen AK, Keil T, Roll S, Hauer B, Mauch H, Wahn U, et al. Interferon-gamma release assays improve the diagnosis of tuberculosis and nontuberculous mycobacterial disease in children in a country with a low incidence of tuberculosis. Clin Infect Dis 2007;45:322-328.
29 Cordova J, Shiloh R, Gilman RH, Sheen P, Martin L, Arenas F, et al. Evaluation of molecular tools for detection and drug susceptibility testing of Mycobacterium tuberculosis in stool specimens from patients with pulmonary tuberculosis. J Clin Microbiol 2010;48:1820-1826.
30 Méndez-Echevarria A, González-Muñoz M, Mellado MJ, Baquero-Artigao F, Vecino R, Pérez E, et al. Optimizing interpretation of the tuberculin test using an interferon-gamma release assay as a reference standard. Pediatr Infect Dis J 2011;30:426-428.
31 Haustein T, Ridout DA, Hartley JC, Thaker U, Shingadia D, Klein NJ, et al. The likelihood of an indeterminate test result from a whole-blood interferon-gamma release assay for the diagnosis of Mycobacterium tuberculosis infection in children correlates with age and immune status. Pediatr Infect Dis J 2009;28:669-673.
32 Diel R, Loddenkemper R, Nienhaus A. Evidence-based comparison of commercial interferon-gamma release assays for detecting active TB: a metaanalysis. Chest 2010;137:952-968.
33 Bergamini BM, Losi M, Vaienti F, D'Amico R, Meccugni B, Meacci M, et al. Performance of commercial blood tests for the diagnosis of latent tuberculosis infection in children and adolescents. Pediatrics 2009;123:e419-424.
34 Rangaka MX, Wilkinson KA, Seldon R, Van Cutsem G, Meintjes GA, Morroni C, et al. Effect of HIV-1 infection on T-Cell-based and skin test detection of tuberculosis infection. Am J Respir Crit Care Med 2007;175:514-520.
35 Gennaro ML. Immunologic diagnosis of tuberculosis. Clin Infect Dis 2000;30:S243-S246.
36 Nakamura RM, Einck L, Velmonte MA, Kawajiri K, Ang CF, Delasllagas CE, et al. Detection of active tuberculosis by an MPB-64 transdermal patch: a field study. Scand J Infect Dis 2001;33:405-407.
37 Boehme C, Molokova E, Minja F, Geis S, Loscher T, Maboko L, et al. Detection of mycobacterial lipoarabinomannan with an antigen-capture ELISA in unprocessed urine of Tanzanian patients with suspected tuberculosis. Trans R Soc Trop Med Hyg 2005;99:893-900.
38 Steingart KR, Henry M, Laal S, Hopewell PC, Ramsay A, Menzies D, et al. A systematic review of commercial serological antibody detection tests for the diagnosis of extrapulmonary tuberculosis. Thorax 2007;62:911-918.
39 Mutetwa R, Boehme C, Dimairo M, Bandason T, Munyati SS, Mangwanya D, et al. Diagnostic accuracy of commercial urinary lipoarabinomannan detection in African tuberculosis suspects and patients. Int J Tuberc Lung Dis 2009;13:1253-1259.
40 Starke JR. Diagnosis of tuberculosis in children. Pediatr Infect Dis J 2000;19:1095-1096.
41 Marais BJ, Gie RP, Hesseling AC, Schaaf HS, Lombard C, Enarson DA, et al. A refined symptom-based approach to diagnose pulmonary tuberculosis in children. Pediatrics 2006;118:e1350-1359.
42 Hesseling AC, Schaaf HS, Gie RP, Starke JR, Beyers N. A critical review of diagnostic approaches used in the diagnosis of childhood tuberculosis. Int J Tuberc Lung Dis 2002;6:1038-1045.
43 Wong KS, Huang YC, Lai SH, Chiu CY, Huang YH, Lin TY. Validity of symptoms and radiographic features in predicting positive AFB smears in adolescents with tuberculosis. Int J Tuberc Lung Dis 2010;14:155-159.
44 Andronikou S, Joseph E, Lucas S, Brachmeyer S, Du Toit G, Zar H, et al. CT scanning for the detection of tuberculous mediastinal and hilar lymphadenopathy in children. Pediatr Radiol 2004;34:232-236.
45 Gómez-Pastrana D, Carceller-Blanchard A. Should pulmonary computed tomography be performed in children with

tuberculosis infection without apparent disease? An Pediatr (Barc) 2007;67:585-593.
46 Andronikou S, Vanhoenacker FM, De Backer AI. Advances in imaging chest tuberculosis: blurring of differences between children and adults. Clin Chest Med 2009;30:717-744, viii.
47 De Backer AI, Mortelé KJ, Vanhoenacker FM, Parizel PM. Imaging of extraspinal musculoskeletal tuberculosis. Eur J Radiol 2006;57:119-130.
48 Singh M, Moosa NV, Kumar L, Sharma M. Role of gastric lavage and broncho-alveolar lavage in the bacteriological diagnosis of childhood pulmonary tuberculosis. Indian Pediatr 2000;37:947-951.
49 Zar HJ, Hanslo D, Apolles P, Swingler G, Hussey G. Induced sputum versus gastric lavage for microbiological confirmation of pulmonary tuberculosis in infants and young children: a prospective study. Lancet 2005;365:130-134.
50 Ba F, Rieder HL. A comparison of fluorescence microscopy with the Ziehl-Neelsen technique in the examination of sputum for acid-fast bacilli. Int J Tuberc Lung 1999;3:1101-1105.
51 Steingart KR, Henry M, Ng V, Hopewell PC, Ramsay A, Cunningham J, et al. Fluorescence versus conventional sputum smear microscopy for tuberculosis: a systematic review. Lancet Infect Dis 2006;6:570-581.
52 Marais BJ, Brittle W, Painczyk K, Hesseling AC, Beyers N, Wasserman E, et al. Use of light-emitting diode fluorescence microscopy to detect acid-fast bacilli in sputum. Clin Infect Dis 2008;47:203-207.
53 Siddiqi S, Ahmed A, Asif S, Behera D, Javaid M, Jani J, et al. Direct drug susceptibility testing of Mycobacterium tuberculosis for rapid detection of multidrug resistance using the Bactec MGIT 960 system: a multicenter study. J Clin Microbiol 2012;50:435-440.
54 Kcocagöz T, Altin S, Türkyılmaz Ö, Taş İ, Karaduman P, Bolaban D, et al. Efficiency of TK culture system in the diagnosis of tuberculosis. Diag Microbiol Infect Dis 2012;72:350-357.
55 Kolk A, Hoelscher M, Maboko L, Jung J, Kuijper S, Cauchi M, et al. Electronic-nose technology using sputum samples in diagnosis of patients with tuberculosis. J Clin Microbiol 2010;48:4235-4238.
56 Kim JH, Kim YJ, Ki CS, Kim JY, Lee NY. Evaluation of Cobas TeqMan MTB PCR for detection of mycobacterium tuberculosis. J Clin Microbiol 2011;49:173.
57 Boehme CC, Nabeta P, Hillemann D, Nicol MP, Shenai S, Krapp F, et al. Rapid molecular detection of tuberculosis and rifampin resistance. N Engl J Med 2010;363:1005-1015.
58 Papaventsis D, Ioannidis P, Karabela S, Nikolaou S, Syridou G, Marinou I, et al. Impact of Gen-Probe Amplified MTD test on tuberculosis diagnosis in children. Int J Tuberc Lung Dis 2012;16:384-389.
59 World Health Organization. Molecular line probe assays for rapid screening of patients at risk of multidrug-resistant tuberculosis (MDR-TB). Geneva: World Health Organization, 2008.
60 Graham SM. Treatment of paediatric TB: revised WHO guidelines. Paediatr Respir Rev 2011;12:22-26.
61 Schoeman JF, Van Zyl LE, Laubscher JA, Donald PR. Effect of corticosteroids on intracranial pressure, computed tomographic findings, and clinical outcome in young children with tuberculous meningitis. Pediatrics 1997;99:226-231.
62 World Health Organization. Rapid advice: treatment of tuberculosis in children. World Health Organization, Geneva, Switzerland, 2010.
63 Jassal MS, Aldrovandi GM. 2050: Ending the odyssey of the great white plague. Pharmacol Res 2011;64:176-179.
64 Koul A, Arnoult E, Lounis N, Guillemont J, Andries K. The challenge of new drug discovery for tuberculosis. Nature 2011;469:483-490.
65 Nair N. Childhood tuberculosis: public health and contact tracing. Pediatr Respir Rev 2001;2:97-102.
66 Kochi A, Nunn P, Dye C, Taylor E. Global burden of disease. Lancet 1997;350:142.
67 Gandhi NR, Moll A, Sturm AW, Pawinski R, Govender T, Lalloo U, et al. Extensively drug-resistant tuberculosis as a cause of death in patients co-infected with tuberculosis and HIV in a rural area of South Africa. Lancet 2006;368:1575-1580.
68 Guidance for national tuberculosis and HIV programmes on the management of tuberculosis in HIV infected children: recommendations for a public health approach, 2010. Paris: International Union Against Tuberculosis and Lung Disease, 2010.
69 Migliori GB, Sotgiu G, Gandhi NR, Falzon D, Deriemer K, Centis R, et al. Drug resistance beyond XDR-TB: results from a large individual patient data meta-analysis. Eur Respir J 2012; DOI: 10.1183/09031936.00136312.
70 Seddon JA, Godfrey-Faussett P, Hesseling AC, Gie RP, Beyers N, Schaaf HS. Management of children exposed to multidrug-resistant Mycobacterium tuberculosis. Lancet Infect Dis 2012;12:469-479.
71 Orenstein EW, Basu S, Shah NS, Andrews JR, Friedland GH, Moll AP, et al. Treatment outcomes among patients with multidrug-resistant tuberculosis: systematic review and meta-analysis. Lancet Infect Dis 2009;9:153-161.
72 Ettehad D, Schaaf HS, Seddon JA, Cooke GS, Ford N. Treatment outcomes for children with multidrug-resistant tuberculosis: a systematic review and meta-analysis. Lancet Infect Dis 2012;12:449-456.
73 Ahuja SD, Ashkin D, Avendano M, Banerjee R, Bauer M, Bayona JN, et al. Multidrug resistant pulmonary tuberculosis treatment regimens and patient outcomes: an individual patient data meta-analysis of 9,153 patients. PLoS Med 2012;9:e1001300.
74 Wells CD, Cegielski JP, Nelson LJ, Laserson KF, Holtz TH, Finlay A, et al. HIV infection and multidrug-resistant tuberculosis: the perfect storm. J Infect Dis 2007;196:S86-S107.
75 WHO. Guidelines for the programmatic management of drug-resistant tuberculosis. Geneva: World Health Organization, 2006. http://whqlibdoc.who.int/publications/2006/9241546956_eng.pdf (accessed June 19, 2008).
76 World Health Organization. Report of the meeting on TB medicines for children- July 2008. World Health Organization, Geneva, 2008. http://who.int/selection_medicines/committes/subcommittee/2/en/index.html (accessed June 19, 2012).
77 American Thoracic Society and Centers for Disease Control and Prevention. Targeted tuberculin testing and treatment of latent tuberculosis infection. MMWR Recomm Rep 2000;49:1-51.
78 Lobue P, Menzies D. Treatment of latent tuberculosis infection: an update. Respirology 2010;15:603-622.
79 Comstock G. How much isoniazid is needed for prevention of tuberculosis among immunocompetent adults? Int J Tuberc Lung Dis 1999;3:847-850.
80 Spyridis NP, Spyridis PG, Gelesme A, Sypsa V, Valianatou M, Metsou F, et al. The effectiveness of a 9-month regimen of isoniazid alone versus 3- and 4-month regimens of isoniazid plus rifampin for treatment of latent tuberculosis infection in children: results of an 11-year randomized study. Clin Infect Dis 2007;45:715-722.

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