PAEDIATRIC TUBERCULOSIS

A REMAINING CHALLENGE IN MODERN MEDICINE

Ingebjørg Hagen Agøy

Veiledere: Monica Thallinger (MD, Barnemedisinsk avdeling, OUS) og Ketil Størdal (overlege/forsker, Dr. med., Folkehelseinstituttet)

Prosjektoppgave ved det medisinske fakultet

UNIVERSITETET I OSLO

29.09.2016

Abstract

Largely ignored by the global community, paediatric tuberculosis is a major health challenge. The clinical course of disease, presentation and diagnostics of TB in children differs from adults and poses specific obstacles making paediatric TB hard to suspect, diagnose and treat. Symptoms are often insidious and non-specific. Children are more vulnerable to severe TB disease, and this is true especially for infants under 2 years and immunocompromised children. Proper evaluation and diagnostics is even more problematic in these children as their immune systems are not fully competent. New diagnostic tools and tests are being developed; many of these are not adapted to children and not available in high-endemic, low resource settings. To achieve the goal of no TB deaths in children, private and governmental health authorities have to work together in a joint effort to enhance knowledge of the specifics of child TB, as well as improve the access to child-adapted tools and tests.

INTRODUCTION

Though not as common in the developed world as it used to be, tuberculosis (TB) is one of our time's biggest health challenges. Especially in children, the difficulties concerning the clinical manifestations and diagnostics of TB are substantial. Some children develop no signs of TB disease. In those who are symptomatic, the symptoms are often atypical and nonspecific, and might mimic a series of other conditions. Diagnosing paediatric TB is especially demanding, as children with TB often have a small bacillary load (paucibacillary) and children may also have problems producing satisfactory samples for diagnostic testing. Despite these intricacies, there has been little research and interest throughout the global community concerning the particular aspects of TB in children. This article will outline the specifics of clinical presentation and diagnostics of paediatric tuberculosis, and discuss the associated challenges and obstacles.

METHODS

TB disease is an extensive area, and a number of primary studies and reviews are published, as well as international, governmental and NGO reports, covering TB in general and paediatric TB specifically. This large amount of literature means that creating any systematic overview would be an overwhelming task, and it is beyond the scope of this assignment to do so. My aim is to create a general review of clinical presentation and diagnostics of paediatric TB, focusing on the specific challenges concerning paediatric TB as opposed to adult TB. Prevention and treatment of paediatric TB are important and problematic topics which deserve their own reviews, and I have thus chosen to omit these topics in this assignment. TB in children co-infected with HIV and drug resistant TB are issues I will touch upon only briefly. I have chosen to limit my literature search to works published from 2005 onwards. I have reviewed primary studies, review articles and reports from organisations, with use of different databases to obtain literature; PubMed, MedLine and Google Scholar being the major ones.

NATURAL COURSE OF TB INFECTION

The microorganism responsible for tubercular disease is the bacterium *Mycobacterium tuberculosis*, belonging to the Mycobacterium genus. *M. tuberculosis* bacteria are weakly gram-positive, strongly acid fast, aerobic rods. They have a complex, lipid-rich cell wall, making the bacteria resistant to several disinfectants, detergents and common antibiotics. The complexity of the cell wall makes the bacteria fastidious and slow growing, only dividing

every 15-20 hours. Humans are the only natural reservoir of *M. tuberculosis* and the bacterium is an intracellular pathogen that may establish lifelong infection (1).

The most common route of infection with *M. tuberculosis* is through aerosolized droplets inhaled into the lungs. Once the bacteria arrive in the lungs, all patients will have an inflammatory reaction, which may cause no or only mild symptoms. Depending on age and other factors influencing immune function, the infection can develop into active disease, either in the lungs or in other parts of the body. Alternatively, the TB bacteria may lie dormant for the rest of the individual's life, or become reactivated at a later stage in life (latent disease). In the *Pathogenesis* section of this paper, I will go into more detail on the pathogenesis of infection, as well as the multiple factors that contribute to the higher proportion of atypical and progressive disease in children compared to adults. This is one of the main challenges in paediatric TB, as it makes disease in children harder to recognise and diagnose.

DISEASE BURDEN AND EPIDEMIOLOGY

According to the World Health Organisation (WHO), TB mortality has fallen by 47% since 1990, with nearly all of that improvement taking place since 2000, when the *Millennium Development Goals* (MDGs) were set. Goal 6c aimed to halt and reverse the incidence of TB by 2015, and TB prevalence and mortality rates should be halved compared to their 1990 levels. Effective diagnosis and treatment of TB has saved an estimated 43 million lives between 2000 and 2014. The *End TB strategy* (WHO) hopes to reduce the number of deaths from TB by 90% by 2030, to cut the number of new cases by 80%, and ensure that no family is burdened with catastrophic costs due to TB (2). There has been an increased focus on paediatric TB in later years, and in 2013, WHO, together with several partners, developed *Towards Zero Deaths*, a roadmap for combating tuberculosis in children, where they outline several key actions for reaching zero tuberculosis deaths among children (3).

A third of the world's population is infected with *M. tuberculosis* and once every 4 minutes a child dies from TB. In the annual tuberculosis report from 2015, WHO estimates that 1 million children fell ill with TB in 2014, and 140 000 children died (2). Dodd et al. estimate that in 2010, 22 high burden countries harboured more than 80% of TB infected individuals. There were more than 53 million latent infections among children under 15 years old in 2010. If a child has a TB positive mother, or other close household contact, the risks of the child getting infected is high. More than 15 million children less than 15 years old share households with infected individuals, and more than 10 million children are orphans because their parents died of TB (4, 5). It is estimated that about 10-60% of children with TB are co-infected with HIV (6).

There is no systematic screening for TB in most low resource countries, where TB prevalence is highest. Prevention of TB disease is available as a vaccine, *the Bacillus Calmette-Guérin* (BCG) and as *isoniazid preventive therapy* (IPT). However, the BCG vaccine has only limited efficacy, especially for adult pulmonary TB, and mainly protects against the most severe forms of paediatric TB (e.g. meningitis) (7, 8). WHO recommends that children under 5 years of age who are household contacts or close contacts of people with TB, and who are asymptomatic of TB themselves, should be given 6 months of IPT (9). IPT is showed to reduce the risk of developing active TB by 60%. However, uptake and implementation by *national TB control programs* (NTPs) is poor, and Tadesse et al. found that only about 64% of children eligible for IPT were offered treatment (10).

NTPs are also limited by lack of resources, knowledge and interest to work with paediatric TB. They have routinely been reporting only smear-positive cases, which are less common in children (3). NTPs may also miss cases where patients seek care in other facilities, either public or private, and there is a difference in reporting between private and public health facilities (11). There are poor lateral data linkages between NTPs and other programmes, and not all cases seen in public are reported to the NTP authorities (12). Limited knowledge of disease pathology and natural course of infection among physicians lead to low clinical suspicion and missed diagnosis (12). Under-reporting of TB cases is a major problem, and Dodd et al. estimate that only about 35% of cases in the 15 countries that were reporting notifications in 2010 were detected (4). Poverty and poor access to health care may lead to missed cases and TB may be harder to detect in malnourished children (12).

RISK FACTORS FOR TB INFECTION

Kadiatu is 4 years old and lives in a remote rural village in Sierra Leone. She is small for her age and her mother is worried that she cannot afford enough food for her four children. For several weeks, Kadiatu has been sick, with a poor appetite, fatigue and a cough. Kadiatu's mother took her to the village doctor, where she got some advice and some local herbs to give her daughter. The herbs had little effect, and after a couple of weeks her mother brought her to the local clinic where she was started on Plumpy Nut, a high calorie food supplement to treat malnutrition. Kadiatu has little interest in food, and the Plumpy Nut does not help much. Kadiatu is then prescribed a course of antibiotics for pneumonia. The antibiotics seemed to improve her condition temporarily, but 7 days after Kadiatu finished the course, the condition is the same as before treatment.

Children in exposed areas face a number of risk factors for infection with *M. tuberculosis.* In their *Guidance for national tuberculosis programmes on the management of tuberculosis in children* from 2014, WHO presents four key risk factors for infection with TB:

1) Household contact with a newly diagnosed smear-positive case,
2) Age less than 5 years,
3) HIV infection, and
4) Severe malnutrition (9).

The immune system of infants is not fully developed and they are thus more vulnerable for infection. This is especially true for HIV infected children, malnourished children and the very young.

RISK FACTORS FOR PROGRESSION OF DISEASE

Most children infected with *M. tuberculosis* will not go on to develop active disease. The most important factors that determine whether active disease will develop or not is age and immune system function, as well as time since infection (13). In immunocompetent older children and adults, the risk of progressing to active disease is only 5-10% (14, 15). However, in the two first years of life, there is a larger risk of disease progression and extrapulmonary manifestations (15). Infants are at highest risk, but the risk is significantly reduced in the second year of life. However, most children are infected when they are older than 2 - 3 years, so even though they have low risk of progression (if they are immunocompetent), they still contribute to a considerable percentage of total disease burden (14).

Immunocompetent children infected between 5 and 10 years are at the lowest risk of disease progression after primary infection (14). Children with untreated HIV infection and/or other forms of compromised immunity have a higher risk of progression, which is comparable to the risk in infants under 2 years old (14). More transient immunosuppression, caused by common childhood diseases such as measles, may also facilitate rapid progression of disease (16).

PATHOGENESIS AND CLINICAL MANIFESTATIONS OF TB

Kadiatu's mother brings her daughter back to the local clinic for the third time. Several weeks of treatment for malnutrition have not improved the condition, and by now, Kadiatu has been sick for almost two months. The physician who examines her can see that she is emaciated, her skin is hanging loose from her bones and her cheeks are hollow. She is fatigued and half asleep during the examination. When the physician auscultates her chest he can hear wet rales. When questioned, Kadiatu's mother explains that none of her other children have been sick, though she herself has had a cough and has been feeling tired for several months.

Primary infection

Although more than 98% of TB infections occur through inhalation of infectious droplets to the lungs, other possible entry points may be through the GI tract, skin, mucous membranes and conjunctiva, or through congenital infection (17). As few as 5 bacilli inhaled in an aerosol are thought to be enough to establish an infection focus (13, 14). The presence of TB bacilli in the lungs will cause a small inflammatory reaction, **a primary focus** (**Ghon focus**). Often, this is accompanied by involvement of the draining lymph nodes of the area and, together, this is called a **Ghon** or **primary complex** (18). In 95% of people infected, the primary complex will, during the course of about 2 to 12 weeks, go on to be encapsulated; resulting in a perifocal area of granulomatous inflammation. Occult haematological dissemination may occur early in infection, before cellular immunological mechanisms cause the granuloma to undergo caseous necrosis, fibrosis, calcification and healing (14, 17).

Box 1. Main challenges with presentation

- may be asymptomatic
- variable manifestations, may be atypical presentation.
- often wrongly diagnosed as other disease
- different pathogenesis and symptoms in infants, children and adolescents, compared to adults

Adult-type disease

In 95% of people, the primary infection is thus contained, and this initial process causes no or only mild symptoms. Even though an individual shows no signs of clinical disease, there are often viable TB bacteria remaining in the body, and TB infection may be latent for many

years, causing no symptoms. In about 5% of all individuals infected, most often adults or children whose primary infection occurred after 7 years of age, reactivation of disease or inappropriate containment of the primary infection may cause more active disease, commonly called **adult type disease** (13, 17). This typically occurs in the lungs, where cavities with a large number of bacilli are present; **multibacillary disease**. These individuals are the most contagious as they will cough up aerosols containing large amounts of *M. tuberculosis* (14). Common symptoms of adult-type disease are similar in children and adults, with fever, weight loss, productive cough, haemoptysis and night sweats. Radiographic findings include cavitary lesions, typically in the upper lobes (17). Cavities are infrequent in children below 7-10 years.

Primary TB disease

In 5% of infected individuals, most commonly children, the primary infection is not contained and results in progression of the primary complex, causing **primary TB disease** (18). 60-80% of children who develop tubercular disease get pulmonary manifestations (15). TB disease in children has less characteristic features and fewer bacilli than adult type disease, and is thus called **paucibacillary disease** (18). This means that paediatric TB patients usually are not infectious, as they lack cavities with many bacilli, and small children are not able to produce a strong enough cough to spread aerosols effectively. Many children with pulmonary TB have no or only mild symptoms, and older children are more likely to be asymptomatic than infants. Physical findings may be mild compared to radiographic findings (17). Hertting and Shingadia (2014) present the classic triad of symptoms: **reduced appetite, weight loss** and **chronic cough**. Other common symptoms are prolonged fever, night sweats, fatigue and reduced activity (18). General symptoms are often present before pulmonary manifestations, which often become more obvious after 3-7 months (19). Children often present with prolonged pneumonia, and it is not uncommon for a TB diagnosis to be made after a treatment of presumptive bacterial pneumonia has proved inefficient (15, 18).

Pulmonary progressive disease is the most common manifestation of primary TB and is defined by intrapulmonary progression, with enlargement of affected regional lymph nodes. The bronchi may be partially or completely obstructed due to lymphadenopathy, and this may lead to erosion of bronchial walls called endobronchitis. External compression of bronchi results in segmental lesions caused by localised atelectasis and hyperinflation of neighbouring lung tissue (17). Complications from lymphadenopathy are most common in children less than 5 years, because of small airway size combined with exuberant lymph node enlargement (14).

In children less than 2-3 years, or in immunocompromised children, the primary focus usually continue to grow even after development of cellular immunity (13). This may cause local progression from the primary focus, as it may undergo central caseation and

liquefaction, and may empty into the bronchi resulting in further spread. This is known as **progressive pulmonary primary tuberculosis** or a **complicated Ghon focus** (13, 17). Progressive pulmonary primary disease presents with failure to gain weight or weight loss, anorexia, fatigue, low-grade fever, rales and intermittent cough (17).

Extrapulmonary disease

Progression of TB disease outside of the lungs is called **extrapulmonary TB** and constitutes 10-25% of all paediatric TB (17, 20, 21). Progression of disease beyond the lungs also occurs more frequently in younger children, and they are more likely to have involvement of distal lymph nodes. Progression to neighbouring structures such as the pleural space, mediastinum, oesophagus and pericardium may sometimes occur by local spread, though most often progression to these sites is through the bloodstream (haematogenous spread). This usually occurs early, but may occur at any time during infection, especially if treatment has not been commenced (17). The most common extrapulmonary manifestations are superficial **lymphadenopathy** (67%), **central nervous system** (13%), **pleural** (65%), **miliary/disseminated** (5%) and **skeletal** (4%) TB (15).

Superficial lymphadenitis is the most common site of extrapulmonary disease, comprising 44-67% of extrapulmonary TB. It is more common in children than adults, and usually affects the cervical and submandibular lymph nodes. The most common presentation is non-tender or minimally enlarged lymph nodes (17).

Tuberculous meningitis is the most severe form of TB and usually affects children under 2 years of age. It often presents together with miliary TB, usually within 3-6 months of initial infection. The presentation may be acute, but is usually indolent and the most common presenting symptoms are high-grade fever, vomiting, lethargy, headache, and seizures (17). Focal neurological symptoms often follow, together with altered consciousness and regression of developmental milestones (22).

Miliary TB is due to lymphohematogenous spread of bacteria and usually involves lesions in multiple organs. It has a similar severity as TB meningitis and may present acutely, though usually presents as weeks of fever, cough, anorexia, weight loss and malaise before diagnosis (15, 17). See *table 1* for an overview of the different types of paediatric TB and common symptoms and signs.

Table 1. Clinical manifestations of TB in children (adapted from Cruz et al. and Feja et al.) (15, 17).

Manifestation	Common symptoms	Signs	Manifestations on diagnostic tests
Thoracic TB			
Pulmonary TB	Prolonged fever, weight loss, night sweats, productive cough, haemoptysis, fatigue, reduced activity.	Rales, wheezing, fremitus, dullness to percussion, decreased breath sounds, sputum production.	Chest radiograph: Intrathoracic lymphadenopathy, parenchymal changes. Cavitation and erosions.
Pleural TB	Thoracic pain, cough, fatigue, dyspnoea, anorexia, fever.	Dullness to percussion, diminished breath sounds.	Chest radiograph: Unilateral pleural effusion. Parenchymal finding in approximately ½ of patients.
Pericardial TB	Dyspnoea, cough, fever, weight loss, chest pain.	Hepatomegaly, jugular vein distention, pulsus paradoxus, pericardial friction, tamponade physiology, haemodynamic shock.	Cardiomegaly, pleural effusions, pulmonary infiltrates. Lymphadenopathy. Echocardiography: effusions, thickening of the pericardium and adhesions.
Extrapulmonary TB (10-25% of paediatric TB cases)			
Superficial lymphadenopathy (10-15%[1])	Fever, fatigue, failure to thrive.	Enlarged lymph nodes, usually without tenderness, erythema or warmth. Usually throat/neck nodes." Dry ulceration", pus development.	Chest radiograph abnormalities in 30-40% .
CNS (0.5-2%[2]) (Meningitis, tuberculomas, tuberculous abscesses. Increased intracranial pressure.)	Headache, nausea, fussiness, fever. Cranial nerve palsies, meningeal irritation. Altered consciousness. Coma.	Nuchal rigidity, cranial nerve findings, hemiparesis**.**	Hydrocephalus on CT, parenchymal disease (tuberculomas). 40-86% of chest radiographs abnormal. Abnormalities in CSF.
Miliary/disseminated (1-2%[1])	Fever, cough, weight loss, anorexia, night sweats, malaise, respiratory problems.	Pyrexia, hepatomegaly, abnormal lung examination, splenomegaly, lymphadenopathy, severe illness.	Miliary pattern in chest radiograph, with bilateral multiple, small nodules. Lymphadenopathy, cavitation. Abscesses/granulomas in affected organs.
Skeletal (1-2%[1])	Spondylitis, arthritis, osteomyelitis.	Focal signs of infection; tenderness to palpation, swelling, diminished range of motion, bone pain, pathological fractures.	Evidence of spondylodiscitis, arthritis, osteomyelitis. Chest radigograph abnormalities in 50%.
Cutaneous (<1%[1])	Systemic involvement rare. Skin lesions.	Different kinds of skin lesions, depending on type of cutaneous TB.	Chest radiographs abnormal in 10-20%.

Abdominal (tuberculous enteritis, TB peritonitis)	Chronic abdominal pain, weight loss, anorexia, vomiting, changed bowel habits (23).	Abdominal distention, «doughy» abdomen, ascitic fluid, abdominal mass (psoas abscess).	Lymphadenopathy on CT or ultrasonography. Calcification and rim enhancement of lymph nodes. Chest radiograph abnormalities in 50-75%.
Renal (rare), (hydronephrosis, uretral strictures)	Constitutional symptoms uncommon. Fever seen in 30%. Urinary urgency/frequency, dysuria, flank pain.	Gross haematuria.	Abnormalities on intravenous pyelogram (90%), Hydronephrosis and/or urethral structures. Abnormal chest radiographs in 50%. Pyuria plus haematuria with sterile urine cultures.
Congenital/genitourinary tract (rare)	*Maternal symptoms:* cough, weight loss, malaise, haemoptysis. Neonatal complications.	Prematurity, low birth weight, perinatal mortality.	Radiological investigations not usually performed during pregnancy.
	Neonatal symptoms: may mimic bacterial sepsis. Difficulty breathing, fever, abdominal distention, lethargy.	Hepatosplenomegaly, respiratory distress, lymphadenopathy, failure to thrive, ear discharge (24).	Chest radiographs abnormal in almost all children, over 50% with miliary pattern. Hepatic biopsy culture yield of over 90%.

[1] Percentage of paediatric TB cases (15, 17).
[2] In untreated children with TB (15).

DIAGNOSING TB IN CHILDREN

The physician is worried that Kadiatu might have tuberculosis and he asks her mother to bring Kadiatu to the local hospital which is about 5 km away. The hospital physician wants to do more tests, but he has limited access to diagnostic tools and Kadiatu is too young and too weak to be able to cough up sputum for smear and culture. The regional hospital, which has an x-ray machine, is too far away for Kadiatu and her mother. Kadiatu has deteriorated throughout the last weeks, and the physician is afraid of what will happen if she does not get treated soon. He chooses to start her on medication for TB.

Proper and early diagnosis of TB in children is important, as children are more at risk of rapidly progressing disease, more severe disease and extrapulmonary manifestations (16). However, the diagnosis of paediatric TB is demanding, and a high proportion of children show atypical features. When the child presents to the doctor, the symptoms are often vague or nonspecific, and the diagnosis of TB is usually not made at the first consultation. Many children will initially receive a course of antibiotics for presumptive bacterial

pneumonia and/or treatment for malaria. TB infection may only be suspected if symptoms of pneumonia, fever, weight loss and fatigue persists or are only temporarily relieved by the initial treatment (25). The diagnosis is often based on a clinical triad of **radiographic findings**, a positive **tuberculin skin test** (TST) and an **epidemiological link to an adult source with suspected or confirmed TB** (15).

WHO guidelines from 2014 recommend the following diagnostic approach:

1. History (including history of TB contact and symptoms)
2. Physical examination (including growth assessment)
3. Tuberculin skin testing (see *Box 3.)*
4. Bacteriological confirmation whenever possible
5. Investigations relevant for pulmonary or extrapulmonary TB
6. HIV testing in high prevalence areas (9)

History and clinical examination

Evaluation of the clinical picture is essential when considering the diagnosis of TB in a paediatric patient. A full clinical examination should be conducted, looking for signs of both pulmonary and extrapulmonary TB. As before mentioned, the symptoms and signs may be atypical and may also depend on the type of manifestation of TB. An evaluation of the child's growth and nutritional status (weight and height, WHO Z score) is important, as most children with TB experience weight loss. The clinician should take a careful history and try to identify any TB contacts, time of exposure, especially within the last 12 months, and type of TB at source (25). An investigation of the duration and progression of any symptoms present is also essential. For children under 2-3 years of age, parents or caretakers are usually the source of infection. However, once the children get older and start moving around in the community, a substantial proportion of transmission occurs outside the household. In high endemic areas it is documented that most transmission occurs outside the household and thus make it difficult to trace transmission or get an appropriate history of contact. Active transmission, as well as preventive therapy, is often neglected due to limited resources and the high number of adults with TB (21).

Diagnostic tests and procedures

An array of tests and procedures to assist in the diagnosis of TB exist. The tests range from **detection of TB bacteria in biological samples**, such as **sputum** and **gastric aspirates,** to **image based technologies** and **immunological tests** such as **TST** and **Interferon Gamma Release Assays (IGRAs)**. New **nuclear acid amplification tests**, such as **GeneXpert**, are promising as they are able to rapidly identify TB bacteria as well as resistance to certain antibiotics. See *table 2* for an outline of different tests and their main challenges.

There are several challenges with the diagnostic tests when it comes to diagnosing paediatric TB. Most of the tests require laboratory facilities with expensive equipment and trained personnel, and few of the tests are available in resource limited settings. The often paucibacillary nature of the disease makes it difficult to obtain adequate samples for microscopy and culture. Also, young children have difficulties coughing up adequate sputum samples. Several of the procedures are uncomfortable for children and require them to be hospitalised or repeatedly come to the hospital/clinic. There is also a lack of research into new tests, as well as into the diagnostic value of the various existing tests when it comes to diagnosing childhood TB. Generally, most of the tests have a lower specificity and sensitivity in children than in adults (26).

Box 2. Main diagnostic challenges

- atypical presentation
- often paucibacillary disease
- hard to produce adequate sputum samples for testing
- challenges with extrapulmonary disease
- lack of equipment, electricity, health workers
- testing not up to date
- lack of diagnostic tools
- tests not adapted for children
- HIV co-infection and malnourishment

TB in HIV positive, malnourished or otherwise immunocompromised children

TB in HIV-positive children and in children with malnutrition is often atypical and might mimic other disease, including opportunistic infections, and thus represents a specific diagnostic challenge. HIV-infection makes TB harder to diagnose and HIV can mask symptoms and signs of TB. Typical symptoms of TB, such as cough, dyspnoea and fatigue, may be poorly predictive of TB in HIV-positive children (22). Diagnostic tests are generally also more unreliable (27). For instance, opportunistic infections will make chest x-rays less specific and immunosuppression makes TSTs less sensitive. As a consequence, these tests will more often be falsely negative under these conditions. HIV testing is often appropriate as part of the initial investigation of a child in high prevalence areas (8, 26).

Box 3. Tuberculin skin testing (TST)

For a long time, the tuberculin skin test has been the standard method for determining if an individual is infected with *M. tuberculosis*. Tuberculin is injected intradermally on an individual's forearm and recruitment of previously sensitised T lymphocytes results in an inflammatory infiltrate than can be measured as skin induration in millimetres. The induration reaches its maximum size 48-72 hours after injection and the diameter needs to be measured by trained personnel within this period (22).

Definition of a positive test depends on the age and immune status of the individual, the TB prevalence in that area, exposure to TB etc.. Generally, an induration of >5 mm is considered as positive in immunocompromised individuals or individuals with a close TB contact; > 10 mm is positive in immunocompetent individuals exposed to TB, and > 15 mm is positive in individuals with no known risk and in previously vaccinated children.

There are several problems related to TSTs. The test is not able to differentiate active disease from latent. There is a high rate of false positives and negatives. For instance, the test may be falsely positive if the child is BCG vaccinated, has undergone multiple TSTs (booster effect) or is exposed to environmental mycobacteria. 10-40% of immunocompetent children with culture proven TB have a negative initial skin test (18, 22). The test is especially unreliable in HIV positive and malnourished children (26). Also, the test requires access to refrigerators, is operator dependent, and requires at least two visits to a healthcare centre (22).

Table 2. Main diagnostic tests and procedures in the diagnosis of childhood TB, and their main challenges.

Test/ procedure	Characteristics	Main challenges
Immune reaction tests		
Tuberculin skin test (TST)/ Mantoux test	See box 3. Measures skin induration on forearm after injection of tuberculin.	See box 3.
IGRA (interferon gamma release assay)	Immunological test that detect TB antigens in blood. Does not require repeated visits to healthcare centre. Previous BCG vaccination has little or no effect on results (22).	Not shown to have major advantages over TSTs in terms of sensitivity and specificity. Cannot differentiate active from latent disease. WHO advises against IGRAs in middle and low income countries (9).
Radiological tests		
Chest X-ray	Antero-posterior and lateral chest x-ray to look for pulmonary TB. Lateral projection important for visualisation of posterior lymphadenopathy.	Only 40% sensitivity and 74% specificity in children. Even lower in the HIV infected (18). Hard to differentiate hilar lymphadenopathy from thymus in infants. Need available equipment and trained personnel to operate the machines and interpret the results.

CT	Useful in identifying hilar lymphadenopathy and cavitary disease.	Expensive equipment; needs maintenance and skilled personnel, not widely available.
MRI	To visualise skeletal and soft tissue disease.	
Ultrasonography	To look for pleural or pericardial effusion and lymph nodes.	
Standard tests for direct demonstration of *Mycobacterium tuberculosis*		
Sputum microscopy and culture	Most commonly used. Gold standard. Microscopy of sputum stained to reveal acid-fast bacilli (Ziehl Neelsen staining or fluorochrome staining most commonly used). Culture of bacteria in appropriate growth medium.	May take weeks to months to get results from cultures. Low yield in children; only about 15% are smear positive and 30-40% culture positive (28). Even lower in HIV infected (26). Do not detect paucibacillary or extrapulmonary disease. Hard to get suitable sputum samples, as young children produce only saliva. Chest clapping may help expectoration (25).
Sputum induction	Child inhales nebulized hypertonic saline. This irritates the respiratory mucosa and stimulates coughing and sputum production. Single sample equivalent to 2-3 gastric aspirates (29).	Difficult for young children to produce adequate sputum samples. Requires equipment, trained personnel and infection control measures. Small children do not cooperate when taking the test.
Gastric aspirate/lavage	Useful in young children who cannot produce sputum. Children swallow mucus which pools in the stomach and is collected in morning samples. If done on 3 consecutive days the positive culture yield is 40-92% (18).	Invasive procedure. Required repeated visits or hospitalisation for 3 days. Need trained personnel. Uncomfortable and poorly accepted. Needs laboratory facilities with available chemicals for preparation of the gastric lavage (30).
Nasopharyngeal aspirate	Minimally invasive; catheter inserted through nostril into oropharynx, cough reflex stimulated, secretions aspirated (31). Can be performed at any time of day.	Variable performance. Not widely used. Lower culture yield than gastric aspirate. Smear positive in 8.5-17% and culture-positive in 23-30% (31).
String test	Child swallows gelatine capsule containing string which unfolds in upper part of the intestine. The string is pulled out after 4 hrs, microscopy of secretions.	Most appropriate for older children, who tolerate procedure well. Limited by cost and availability. Not yet widely used.
Stool	Stool contains TB bacteria from swallowed secretions. Easily obtained.	Technically difficult as specimen requires stringent decontamination procedures. Bacterial overgrowth and poor sensitivity (18, 26).
Fine needle biopsy and **image guided biopsies of superficial lymph nodes**	Minimally invasive. Can be performed as outpatient procedure. Specimens suitable for smear microscopy, culture and drug sensitivity testing. Yield might be higher than sputum. Potentially under-utilised	Requires equipment and trained personnel.
Urine	Detecting presence of lipoarabinomannan (LAM), a fatty molecule found in the cell wall of TB bacteria and secreted into urine by active TB. Urine is easily collectible sample. Sensitivity higher in HIV positive children (32).	Needs more research.

Scoring systems		
Score charts, e.g. **Keith Edwards scoring system**	Weigh findings from different diagnostic measures, e.g. duration of illness, nutrition, family history of TB, symptoms and clinical findings. Aids in reaching final diagnosis.	Performance varies, poorest in children with pulmonary TB and the HIV infected (26). Keith Edwards scoring system is effective for diagnosing TB in field conditions, but less effective in chronic conditions where chances of false positive results are high (33).
New methods		
NAATs (nuclear acid amplification tests), e.g. **GeneXpert** (MTB/RIF)	Detects DNA in TB bacteria obtained from different specimens, most commonly sputum samples. Can rapidly (< 2 hrs) identify TB bacteria and resistance to antibiotics (18). Most significant recent advance in TB diagnostics. Twice the sensitivity of smear microscopy (34). WHO recommends that GeneXpert replaces smear microscopy for initial diagnosis of HIV associated TB and MDR pulmonary TB (35).	Expensive, requires laboratory facility and trained personnel. Reliance on suitable samples limits utility. Nicol et al. (2011) recommend two sputum samples. Less sensitive for smear-negative TB than in samples from adults (36).
Liquid culture systems (e.g. **MGIT BACTEC, BACT/Alert**)	Laboratory culture methods, including use of automated liquid culture systems. Decreases turnaround time and increases recovery rate as compared to standard solid culture medium. Also tests for drug sensitivity.	Expensive, requires equipment and laboratory facilities. Trained personnel.
Genome-wide expression	Genes expressed differentially in individuals with active TB disease compared to latent TB or other diseases. Sweeney et al. (2016) found a set of three genes in whole blood that is diagnostic for active TB. Potential clinical application for diagnosis and monitoring treatment response (37).	Needs laboratory validation before it can be used in a clinical setting (37).

After about a week of TB medication, Kadiatu is more interested in food, she starts to gain some weight and she seems brighter and more alert. In a couple of more weeks she has regained much of her energy, she smiles, laughs and plays with the other children on the ward. After four weeks in the hospital, her condition has improved so much that she is sent home to continue the oral medication for a total duration of treatment of 6 months.

CONCLUSION

Tuberculosis in children has specific characteristics that are important to understand for health personnel working with clinical medicine. These characteristics apply to both natural course of infection and manifestation of disease; one of the main reasons for the differences being the underdeveloped immune system of young children. This also makes young children more likely to experience progressive and serious disease, which makes more focus on paediatric TB essential. There is a substantial lack of research into new tools for diagnosing TB in children, and many of the existing tools and tests are not optimal in children and/or they are not available in resource-limited settings.

Without more knowledge of these characteristics, combating paediatric TB is going to remain a difficult and intangible task. Even though there has been increasing attention on child TB in later years, the disease is still largely ignored in children. As a result of this, many children will be infected with TB and will die of a disease that may be prevented with appropriate diagnosis and treatment.

The global community, as well as national and regional health authorities, have to stop shutting their eyes on the situation and start focusing on appropriate means of facing this challenge. More funds need to be allocated to research into identifying the symptomatology of paediatric TB disease and to improve existing diagnostic tools, as well as developing new ones. The diagnostic tools have to be made available in low resource settings, at an affordable cost. Sharing of knowledge, and training of health professionals in recognising paediatric TB, is essential to be able to localise cases. Increased collaboration between governmental and private actors, both nationally and globally, will lead to improved case notification systems and a more complete database of information. The road towards zero paediatric TB deaths, as WHO envisioned in their 2013 document, is still long. However, with an increased global effort it may be achievable in the future.

REFERENCES

1. P. R. Murray PhD KSRP, M. A. Pfaller MD. Mycobacterium. Medical Microbiology. 6th ed. Philadelphia (PA): Mosby Elsevier; 2008. p. 278 - 81.
2. World Health Organization. Global tuberculosis report 2015. Geneva: 2015 Contract No.: WHO/HTM/TB/2015.22.
3. World Health Organization: Roadmap for childhood tuberculosis: towards zero deaths. Geneva: 2013 Contract No.: WHO/HTM/TB/2013.12.
4. Dodd PJ, Gardiner E, Coghlan R, Seddon JA. Burden of childhood tuberculosis in 22 high-burden countries: a mathematical modelling study. The Lancet Global health. 2014;2(8):e453-9.
5. Stop TB Partnership Geneva: Stop TB Partnership; [cited 2016 22.05.2016]. Available from: http://www.stoptb.org/.
6. Venturini E, Turkova A, Chiappini E, Galli L, de Martino M, Thorne C. Tuberculosis and HIV co-infection in children. BMC infectious diseases. 2014;14(1):1-10.
7. Davenne T, McShane H. Why don't we have an effective tuberculosis vaccine yet? Expert Review of Vaccines. 2016;15(8):1009-13.
8. Brigden G, Furin J, Van Gulik C, Marais B. Getting it right for children: improving tuberculosis treatment access and new treatment options. Expert review of anti-infective therapy. 2015;13(4):451-61.
9. WHO. World Health Organization. Guidance for national tuberculosis programmes on the management of tuberculosis in children - 2nd ed. . Geneva: WHO, 2014 Contract No.: WHO/HTM/TB/2014.03.
10. Tadesse Y, Gebre N, Daba S, Gashu Z, Habte D, Hiruy N, et al. Uptake of Isoniazid Preventive Therapy among Under-Five Children: TB Contact Investigation as an Entry Point. PloS one. 2016;11(5):e0155525.
11. Coghlan R, Gardiner E, Amanullah F, Ihekweazu C, Triasih R, Grzemska M, et al. Understanding Market Size and Reporting Gaps for Paediatric TB in Indonesia, Nigeria and Pakistan: Supporting Improved Treatment of Childhood TB in the Advent of New Medicines. PloS one. 2015;10(10):e0138323.
12. Shakoor S, Qamar FN, Mir F, Zaidi A, Hasan R. Are TB control programmes in South Asia ignoring children with disease? A situational analysis. Archives of disease in childhood. 2015;100(2):198-205.
13. Marais BJ, Donald PR, Gie RP, Schaaf HS, Beyers N. Diversity of disease in childhood pulmonary tuberculosis. Ann Trop Paediatr. 2005;25(2):79-86.
14. Marais BJ, Gie RP, Schaaf HS, Beyers N, Donald PR, Starke JR. Childhood pulmonary tuberculosis: old wisdom and new challenges. American journal of respiratory and critical care medicine. 2006;173(10):1078-90.
15. Cruz AT, Starke JR. Clinical manifestations of tuberculosis in children. Paediatric respiratory reviews. 2007;8(2):107-17.
16. Cruz AT, Starke JR. Treatment of tuberculosis in children. Expert review of anti-infective therapy. 2008;6(6):939-57.
17. Feja K, Saiman L. Tuberculosis in children. Clinics in chest medicine. 2005;26(2):295-312, vii.
18. Hertting O, Shingadia D. Childhood TB: when to think of it and what to do when you do. J Infect. 2014;68 Suppl 1:S151-4.
19. Marais BJ, Schaaf HS. Tuberculosis in children. Cold Spring Harbor perspectives in

medicine. 2014;4(9):a017855.
20. Santiago B, Blazquez-Gamero D, Baquero-Artigao F, Ruiz-Contreras J, Bellon JM, Munoz-Fernandez MA, et al. Pediatric Extrapulmonary Tuberculosis: Clinical Spectrum, Risk Factors and Diagnostic Challenges in a Low Prevalence Region. The Pediatric infectious disease journal. 2016.
21. Marais BJ, Gie RP, Schaaf HS, Hesseling AC, Enarson DA, Beyers N. The spectrum of disease in children treated for tuberculosis in a highly endemic area. The international journal of tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease. 2006;10(7):732-8.
22. Chiappini E, Lo Vecchio A, Garazzino S, Marseglia GL, Bernardi F, Castagnola E, et al. Recommendations for the diagnosis of pediatric tuberculosis. European journal of clinical microbiology & infectious diseases : official publication of the European Society of Clinical Microbiology. 2016;35(1):1-18.
23. Bhargava DK. Abdominal Tuberculosis: Current Status. Apollo Medicine 2007;4(4):287-91.
24. Mathivha KT, Velaphi S. Characteristics of infants exposed to maternal tuberculosis and chemoprophylaxis using 3 months of isoniazid and rifampicin. Paediatrics and international child health. 2016:1-6.
25. Diagnosis of tuberculosis in children Médecins Sans Frontières: Tuberculosis Practical guide for clinicians, nurses, laboratory technicians and medical auxiliaries La Plaine Saint-Denis Médecins Sans Frontières, Partners In Health; 2014. p. 58-66.
26. Medécins Sans Frontières: Out of the Dark: Meeting the Needs of Children with TB. Geneva: Medécins Sans Frontières, 2011. Report No.
27. Oberhelman RA, Soto-Castellares G, Gilman RH, Castillo ME, Kolevic L, Delpino T, et al. A Controlled Study of Tuberculosis Diagnosis in HIV-Infected and Uninfected Children in Peru. PloS one. 2015;10(4):e0120915.
28. Swaminathan S, Rekha B. Pediatric tuberculosis: global overview and challenges. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America. 2010;50 Suppl 3:S184-94.
29. 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(9454):130-4.
30. Baghaei P, Tabarsi P, Farnia P, Radaei AH, Kazempour M, Faghani YA, et al. Utility of Gastric Lavage for Diagnosis of Tuberculosis in Patients who are Unable to Expectorate Sputum. Journal of Global Infectious Diseases. 2011;3(4):339-43.
31. Owens S, Abdel-Rahman IE, Balyejusa S, Musoke P, Cooke RP, Parry CM, et al. Nasopharyngeal aspiration for diagnosis of pulmonary tuberculosis. Archives of disease in childhood. 2007;92(8):693-6.
32. Kroidl I, Clowes P, Reither K, Mtafya B, Rojas-Ponce G, Ntinginya EN, et al. Performance of urine lipoarabinomannan assays for paediatric tuberculosis in Tanzania. The European respiratory journal. 2015;46(3):761-70.
33. Sarkar S, Paul DK, Chakrabarti S, Mandal NK, Ghoshal AG. The Keith Edward scoring system: A case control study. Lung India : official organ of Indian Chest Society. 2009;26(2):35-7.
34. Giang do C, Duong TN, Ha DT, Nhan HT, Wolbers M, Nhu NT, et al. Prospective evaluation of GeneXpert for the diagnosis of HIV- negative pediatric TB cases. BMC infectious diseases. 2015;15:70.
35. WHO Information Note 2013: Tuberculosis diagnostics: Xpert MTB/RIF Test
36. Nicol MP, Workman L, Isaacs W, Munro J, Black F, Eley B, et al. Accuracy of the Xpert MTB/RIF test for the diagnosis of pulmonary tuberculosis in children admitted to

hospital in Cape Town, South Africa: a descriptive study. The Lancet Infectious Diseases. 2011;11(11):819-24.
37. Sweeney TE, Braviak L, Tato CM, Khatri P. Genome-wide expression for diagnosis of pulmonary tuberculosis: a multicohort analysis. The Lancet Respiratory medicine. 2016;4(3):213-24.