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Pediatric tuberculosis: Symptoms, prevention and treatment

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Abstract

Tuberculosis (TB) is a prevalent disease in many parts of the world, particularly, in Africa and many South Asian countries. Considering the life-threatening nature of this disease, over the years, many antituberculosis drugs have been developed to prevent, manage, or treat TB. The World Health Organization (WHO) is heavily involved in TB control programs with the objectives to provide guidance for early diagnosis of TB, timely treatment with appropriate antituberculosis medicines with optimum therapeutic dosing. Considering the importance of a 'right dose' in the treatment of a disease, Over the years, WHO has revised the pediatric dosing for TB several times and in 2014 pediatric dosing was adjusted based on the pharmacokinetic (PK) studies as well as safety. However, these dosing recommendations by WHO for the treatment of TB requires more robust PK studies. The objectives of this review are to provide the readers the difference in the etiology of TB disease between adults and children, the diagnosis, prevention and treatment of TB in children especially, in younger children (<2 years of age).

Keywords: Tuberculosis; Children; Prevention and Treatment; Pharmacokinetics

1. Introduction

Tuberculosis (TB) is a common disease in Africa and in many south Asian countries (1). On a global scale, the World Health Organization (WHO) is heavily involved in the TB control program. The main objective of the WHO is to provide guidance for early diagnosis of TB and timely treatment with appropriate anti-tuberculosis medical treatments with the proper dose (2).

Like adults, children are also susceptible to TB. In 2020, it was found that 11% of children aged <15 years of the estimated 10 million cases of TB were affected and 16% of children died of TB disease (230,000 of 1.4 million) (3,4). Children <5 years of age, children with Human Immunodeficiency Virus (HIV), and malnourished children are at high risk for TB (5). Pediatric TB is often undiagnosed and underreported due to poor access to healthcare, late diagnosis and poor disease management (1).

Pediatric TB is a significant global health threat and is one of the top ten causes of death in children (6,7). There are a number of diagnostics, treatment, and preventive innovations that have been developed in the last decade for TB, however, these are out of reach for many children in the world. There is great potential for radical changes in the way all forms of TB are diagnosed, treated and prevented in children. Unfortunately, unless there is continued advocacy and adequate funding and accountability, it could be possible to make great strides toward eliminating TB in children in the next ten years (7).

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As the incidence of tuberculosis (TB) has increased worldwide, it is expected that pregnant women will acquire this infection more frequently. Mycobacterium tuberculosis infection during pregnancy may represent a risk for maternal and neonatal complications. Children born to women with TB have an increased risk of morbidity and mortality in the neonatal period (8).

True congenital tuberculosis is rare, unfortunately the greatest threat to the neonate is the acquisition of tuberculosis infection shortly after birth, which tends to progress rapidly to serious tuberculosis disease in a large proportion of untreated infants. Effective methods for prevention and treatment of the disease are available and inexpensive, but still are not used appropriately in most parts of the developing world (9,10)**.** The clinician caring for pregnant women should be aware of the risk factors for tuberculosis infection and disease and should test women and families according to risk.

The objectives of this review were to describe the symptoms, prevention, screening, diagnosis, monitoring, and treatment of TB in neonates as well as infants and children.

2. Clinical Manifestation of Childhood Tuberculosis

2.1. Perinatal Tuberculosis

2.1.1. Newborns and Mothers

As the incidence of tuberculosis (TB) has increased worldwide, it is expected that pregnant women will acquire this infection more frequently. Mycobacterium tuberculosis infection during pregnancy may represent a risk for maternal and neonatal complications. Children born to women with TB have an increased risk of morbidity and mortality in the neonatal period (11).

TB can be acquired during the perinatal period. Infants may acquire TB by the following means

- Transplacental spread through the umbilical vein to the fetal liver
- Aspiration or ingestion of infected amniotic fluid
- Airborne inoculation from close contacts (family members or nursery personnel) (12).

About 50% of children born to mothers with active pulmonary tuberculosis develop the disease during the first year of life if chemoprophylaxis or Bacille-Calmette-Guérin (BCG) vaccine is not given.

TB bacteria are spread through the air when an infected person coughs, sneezes, or speaks too close to another person. Children can be exposed to TB in several stages: (9)

- When a child comes in contact with a person who has TB. In this child, skin or blood test and a normal chest X-ray indicates no TB and no symptoms.
- When a child has TB bacteria in the body but does not have symptoms. This stage is called 'latent TB infection'. The infected child's immune system causes the TB bacteria to be inactive. This type of TB may be latent for life. Many children infected with M. tuberculosis never develop active TB and remain in the latent TB stage. This child would have a positive TB skin or blood test but a normal chest X-ray and no TB symptoms. Children with latent TB infection cannot spread TB to others.
- When a child has signs and symptoms of an active infection, then this stage is called 'TB disease'. This child would have a positive or negative TB skin or blood test, and testing showing active TB disease in the lungs or another site in the body. Such children can spread the disease if the infection is in the lungs, and it is untreated.

2.2. Symptoms of TB

Children can get TB from different sources such as living with someone who has TB, living in a country where TB is common and having a weak immune system, including from diabetes, HIV, or medicines that can weaken the immune system (13,9). Babies and children are at higher risk. Very young children are more likely than older children to have TB spread through their bloodstream and cause complications such as meningitis (14,11).

Symptoms of TB vary from child to child and are age dependent. The most common symptoms of active TB in younger children include: (1)

- Fever

- Cough
- Chills
- Weight loss
- Poor growth
- Swollen glands (some may begin to discharge fluid through the skin)

The most common symptoms of active TB in older children include: (15-18)

- Cough that lasts longer than 3 weeks
- Fever
- Chills
- Pain in the chest
- Blood in sputum
- Sweating at night
- Weight loss
- Weakness and fatigue
- Swollen glands (some may begin to exude fluid through the skin)
- Decrease in appetite

Certain medical conditions/addictions can increase a person's risk for tuberculosis disease (15-18)

- Metabolic Disease (i.e. Diabetes, obesity, and cardiovascular diseases)
- Weakened Immune System, For Instance HIV And Aids
- Malnourished
- Tobacco Use

2.3. Screening

TB exposure in congregate settings related to neonates is a serious medical and social issue (16-20), (12). TB exposure may happen during the neonatal period, but contact investigations for exposed infants are usually conducted after the neonatal period. Generally, recommendations for screening and managing close contact are different for neonates and children. In Korea, a single Tuberculin Skin Test (TST) at three months after the last TB exposure with Isoniazid, or Isonicotinic Acid Hydrazide (INH) prophylaxis could be used as a main protocol in contact investigations for infants exposed to infectious TB during the neonatal period in congregate settings in Korea (17).

Improving detection of pediatric TB is critical to reducing morbidity and mortality among children. Researchers identified a potential opportunity to increase TB detection by screening children presenting in health care settings. Pediatric TB case finding interventions should incorporate evidence-based interventions and local contextual information in an effort to detect as many children with TB as possible (18-19).

According to the WHO, the following considerations should be given for screening of TB in children and adolescents, with the recognition that children and adolescents have a high risk of developing TB if they come in contact with a person who has TB disease (13,20).

- In order to identify children who have been exposed to TB and to screen them for TB, it is important that their contact information be investigated. Contact investigation requires dedicated human and financial resources, and contact investigation is most efficient if conducted in an active manner at the community or household level.
- Screening approaches are slightly different for children who are in close contact with a person with TB and children living with HIV.
- For close contact of a person with TB:
- Screening tools are symptom screen and/or Chest X-ray (CXR).
- Symptom screen: Cough for more than 2 weeks, fever for more than 2 weeks and poor weight gain (or weight loss) in the past 3 months
- Timing of screening: during contact investigation and follow-up activities.

2.3.1. For children living with HIV

- Screening tool is a symptom screen characterized by current cough, fever, poor weight gain in the past 3 months, or close contact with a person who has TB.
- Timing of screening: every encounter with a health care worker.

Children who screen positive on a TB symptom screen and/ or have an abnormal CXR should be identified as having presumptive TB and evaluated for TB disease.

Children who do not have TB symptoms and have a normal CXR on TB screening should be offered tuberculosis preventive treatment such as Isoniazid, Rifampin, and Rifapentine, if they do not have contraindications.

Screening for TB remains challenging due to the limitations of current diagnostic tests, leading to over-diagnosis and misdiagnosis (21-28). Some of the key aspects to be considered for future development of diagnostic tests for differentiating between LTBI, incipient, subclinical, and Actual TB (ATB) suitable for children, elderly, and high-risk populations are (22-32), (16)

- Use of flow cytometry for simultaneous detection of T cell subsets and their signature cytokines.
- Study on microRNAs and (mRNAs) as diagnostics and therapeutics candidates for TB (22-24), (18).
- Identification of markers not only for diagnostic purposes, but also able to assess the TB progression or reactivation risk.
- A non-invasive approach using urine for the detection of Mycobacterium tuberculosis (MTB) or host-related biomarkers (25-37).
- Use of interferon gamma release assay (IGRA), MTB-specific Aminoglycosides (Ags) or epitopes for development of skin test reagents (21-26).

2.4. Diagnosis

The diagnosis of tuberculosis in children is traditionally based on chest radiography, tuberculin skin testing, and mycobacterial staining/culture, although these investigations may not always be positive in children with tuberculosis. Newer diagnostic methods, such as **P**olymerase **C**hain **R**eaction (PCR) (22,24) and immune-based methods, are increasingly being used, although they are not widely available and have a limited role in routine clinical practice. Diagnostic approaches have been developed for use in resource-limited settings; however, these diagnostic methods have not been standardized and few have been validated (27-28), (12).

The WHO recommends the use of rapid molecular diagnostic tests as the initial diagnostic test in all persons with signs and symptoms of TB (15). Rapid tests include the Xpert MTB/RIF Ultra and Truenat assays. These tests have high diagnostic accuracy and will lead to major improvements in the early detection of TB and drug-resistant TB. Tuberculosis is particularly difficult to diagnose in children (29-30), (25), (21).

Skin or blood tests can be used (like adults) to diagnose TB in children. A chest X-ray, sputum testing, or a biopsy of abnormal glands or other body tissues can also be examined to diagnose TB in children. A TB skin or blood test is advised for children who:

- May have been exposed to TB in the last 5 years
- Has an X-ray that looks like TB
- Has any symptoms of TB
- Comes from a country where TB is common

Yearly TB skin or blood testing should be done on children who have HIV. Furthermore, children who are exposed to high-risk people should be tested every 2 to 3 years.

Globally, it is estimated that one-quarter of the world's population is infected with latent tuberculosis infection (LTBI). Detection of TBI is challenging as the infected individual does not present symptoms. Currently, there is no gold standard for TBI diagnosis, and the only screening tests are tuberculin skin test (TST) and interferon gamma release assays (IGRAs) (31), (16), (9). Interferon Gamma Release Assay (IGRA) is a diagnostic test which detects Interferon gamma (IFN-γ) response produced by T lymphocytes after stimulation by specific antigens [early secretary antigen target 6 (ESAT-6) and culture filtrate protein 10 (CFP-10)] encoded by a genomic segment unique to M. tuberculosis (32-41), (31). However, there is Immunotherapy (33-34) and PCR Testing available (28,24). TBI therapy is a key

intervention for TB control. However, the long-course treatment and associated side effects (35-36), (26) result in non-adherence to the treatment). Additionally, the latent MDR strains are not susceptible to the current TBI treatments, which add a challenge (37-38).

2.5. Diagnosis of Perinatal TB

Perinatal TB is a rare disease, transmitted during pregnancy or postnatal. Its clinical presentation is similar to congenital infections and neonatal sepsis, which remains underestimated and under-diagnosed (39). Perinatal TB is generally diagnosed by the following:

- Culture of tracheal aspirate
- Gastric washings
- Urine
- Cerebrospinal fluid (CSF)
- Chest x-ray and skin testing.

2.6. Miliary TB

Besides latent TB and TB disease, there is another form of TB known as 'Miliary TB'. Miliary TB is predominantly a disease of infants and children, but it has also been noted in adults.

Miliary TB is a rare (1-2% of total TB) but, severe or fatal and disseminated form of TB. Miliary TB results from a massive lymphohematogenous dissemination of Mycobacterium tuberculosis bacilli and is characterized by tiny tubercles evident on gross pathology resembling millet seeds (hence the name miliary) in size and appearance. Miliary TB occurs when bacteria spread through the bloodstream, affecting multiple organs throughout the body. The clinical manifestations of miliary TB are of varied nature and nonspecific, resulting in delayed diagnosis. Clinicians, therefore, have a low threshold for suspecting miliary TB (40). Examination of sputum, body fluids, image-guided fine-needle aspiration cytology or biopsy from various organ sites, needle biopsy of the liver, bone marrow aspiration, and biopsy should be done to confirm the diagnosis of miliary TB (41-42). Cytopathological, histopathological, and molecular testing (expert MTB/RIF and line probe assay), mycobacterial culture, and drug susceptibility testing must be carried out as appropriate and feasible (43-44).

A clinical study (45) reported a 6-day-old female infant with cough and wheezing, whose mother had miliary TB (46). Gastric aspirate smear, tuberculin skin test, blood and sputum culture of the infant were (47) negative. Thoracic computed tomography demonstrated several consolidated patches with diffuse high-density nodular opacities in bilateral lungs. Fiberoptic bronchoscopy was performed to obtain bronchoalveolar lavage fluid, reduce secretion and restore airway patency on 2 days after admission. Mycobacterium tuberculosis was detected by bronchoalveolar lavage fluid Xpert MTB/RIF and rifampicin resistance was negative on 3 days after admission. An appropriate anti-tuberculosis drug was chosen. The infant made a good recovery. Fiberoptic bronchoscopy plays a vital role in diagnosing rapidly and treating perinatal tuberculosis. And may be promoted as an important approach to the management of perinatal tuberculosis.

Miliary TB is a rare and serious infection that must be considered in the differential diagnosis of neonates, with neonatal sepsis unresponsive to conventional antibiotic therapy, especially if combined with radiographic changes and negative cultures. Suspicion should be reinforced if there is a strong epidemiological correlation, especially in countries with high rates of Mycobacterium tuberculosis infection, such as Brazil (48). Timely diagnosis and treatment of this condition are essential to reduce mortality from Perinatal TB, as well as meticulous prenatal care and treatment of maternal TB (49-50).

2.7. Prevention

TB can be prevented by lowering children's risk of exposure to others with the infection (18). Active TB can be prevented by having latent TB diagnosed and treated. The WHO provides the following important tips for the prevention of TB: (51-52).

- Seek medical attention if you have symptoms like prolonged cough, fever and unexplained weight loss, as early treatment for TB can help stop the spread of disease and improve your chances of recovery.
- Get tested for TB infection if you are at increased risk, such as if you have HIV or are in contact with people who have TB in your household or your workplace.
- If prescribed treatment to prevent TB, complete the full course.

- If you have TB, practice good hygiene when coughing, including avoiding contact with other people and wearing a mask, covering your mouth and nose when coughing or sneezing, and disposing of sputum and used tissues properly.

Special measures like respirators and ventilation are important to reduce infection in healthcare and other institutions.

A study (53) provided a brief overview of the natural history of the disease in children to demonstrate the importance of taking a careful TB exposure history. It also provides guidance regarding the diagnosis, treatment and prevention of tuberculosis in children. The management of pediatric cases is not difficult if important differences with adult disease are carefully considered. Prevention strategies include vaccination, pre- and post- exposure prophylaxis, treatment of 'latent' infection, and secondary prophylaxis (provided after completion of TB treatment) (51). Careful risk stratification identifies those at greatest need of preventive therapy following TB exposure. The target population for preventive therapy provision may vary in different settings depending on feasibility and available resources, but all young (aged less than 5 years) and/or immunocompromised children should receive preventive therapy following documented exposure/infection.

Youngui et. al. (53) indicated that the tests for TB have its limitations and the diagnosis of TB relies on an indirect immunological assessment of cellular immune response to Mycobacterium TB antigens using immunodiagnostic testing (54-57), The authors recommended that the children and adolescents who are exposed to TB should receive TB preventive treatment to reduce or stop the progression of the disease (58-61).

2.8. Prevention of Perinatal TB

Perinatal TB may be prevented by universal neonatal BCG vaccination. (62-64) It may curb the incidence of childhood TB or decrease its severity in populations at increased risk of infection. The symptoms and signs of perinatal TB in the neonates can be characterized by acute or chronic illness, fever, lethargy, respiratory distress or non-responsive pneumonia, hepatosplenomegaly, or failure to thrive, but is usually marked by multiple organ involvement. Symptoms and signs are nonspecific. Diagnosis is by culture and sometimes x-ray and biopsy; treatment is with isoniazid and other anti-tuberculous drugs.

Extrapulmonary, miliary and meningeal TB in mothers are high risk factors for congenital TB in neonates. Vertical transmission from mothers with tubercular pleural effusion or generalized adenopathy does not occur. However, there is a lack of scientific literature regarding increased risk of congenital TB if mothers have resistant TB or concurrent HIV infection. Mothers who have completed antitubercular treatment (ATT) before delivery or have received ATT for at least two weeks duration before delivery are less likely to transmit the disease to the newborn as compared to untreated mothers. Antitubercular drugs are found to be safe in pregnancy, except streptomycin in the first trimester. Literature is available regarding the safety of second line antitubercular drugs used for resistant TB in pregnancy, however, a six (6) month regiment is necessary, rendering adherence difficult. (65-70), (51), (7).

2.9. Monitoring

Accurate statistics on pediatric TB cases are difficult to obtain for a multitude of reasons, including under-recognition, challenges in confirming the diagnosis, and under-reporting to national TB programs. The clinical and radiographic manifestations are less specific in children compared to adults, and are often confused with bacterial pneumonia (71-75). Microbiologic confirmation of disease is limited by the paucibacillary nature of TB in children; in general, TB cultures and newer rapid molecular tests are positive in the minority of children, generally <25-40% of children with TB disease. Additionally, there are often logistic challenges in obtaining adequate specimens from young children (76). However, in the era of multi drug-resistant TB (MDR-TB) in which the organism is resistant to isoniazid and rifampin (the two most potent first-line anti-TB agents), there is an increasing need to attempt culture-confirmation on all children suspected of having TB in order to inform treatment decisions. Among children who are started on TB therapy, families struggle with proper dose administration due to the lack of pediatric drug formulations and there are programmatic gaps in notifying the national TB program, leading to under-reporting by the WHO. Yet, with proper management, including timely treatment initiation with appropriate drug dosages, treatment outcomes are generally favorable (77),(46),(6).

Quantifying exposure to drugs for personalized dose adjustment is of critical importance in patients with TB, who may be at risk of treatment failure or toxicity due to individual variability in pharmacokinetics. Traditionally, serum or plasma samples have been used for drug monitoring, which only poses collection and logistical challenges in high-tuberculosis burden/low-resourced areas. Less invasive and lower cost tests using alternative biomatrices other than serum or plasma may improve the feasibility of therapeutic drug monitoring (78-80),(27-30),(25).

Childhood TB has historically been a near-invisible part of the global TB epidemic. This can be attributed to several factors, including a reliance on sputum smear microscopy for diagnosis. Only a few children were historically confirmed microbiologically, leading to poor quantification of the disease burden. Childhood TB lags behind progress in adults in the understanding of disease burden, and also in research and development of diagnosis and treatments. Yet children are particularly vulnerable to developing TB disease after exposure, which can progress to severe forms of the disease, including TB meningitis (TBM) (81). Older children and adolescents can transmit Mycobacterium tuberculosis and so contribute to disease propagation, and children infected with Mycobacterium tuberculosis provide a reservoir for future disease. Thus, addressing child and adolescent TB is essential in the fight towards TB elimination.

A group of Italian experts (82-86) concluded that if suspicion is aroused, it is necessary to promptly undertake all the investigations useful for identifying the disease not only in the newborn, but also in the mother and family contacts because a diagnosis of TB in the family nucleus can guide its diagnosis and treatment in the newborn. If the suspicion is confirmed, empirical treatment should be started. Breast-fed newborns being treated with isoniazid should be given pyridoxine supplementation at a dose of 1 mg/kg/day. Mothers with active-phase TB can breast-feed once they have become smear-negative after having received appropriate treatment (87-96), (52).

2.10. Treatment

Children act as reservoirs of infection out of which future cases develop. Without the successful detection and treatment of TB infection and disease in children, elimination strategies for TB will be ineffective. Tuberculosis (TB) is not only related to infection but also involves pediatric immune factors. Knowledge of the epidemiology, evolution and natural history of childhood TB is essential in understanding which children are the most vulnerable (36). The development of the neonatal immune system is characterized by dynamic transitions from innate to adaptive immunity. Cell-intrinsic developmental changes of both innate and adaptive (antigen-specific) immunity interact differently in early stages of life, result of prenatal programming for limited innate and adaptive immune responses maintaining fetal/maternal tolerance and to promote non-inflammatory processes, such as homeostasis and tissue growth, to the limited time the neonate has for reprogramming of the innate and adaptive immune systems by postnatal exposure for making postnatal metabolic adaptations (11). Researchers reported changes in T-lymphocyte subsets in children with TB who are human immunodeficiency virus (HIV)-negative (97). The virulence of the mycobacterial strain and their genetics, host genetics, BCG vaccination, malnutrition, immunodeficiency are some of the risk factors (36). Primary immune defects, local anatomical factors (TB Meningitis, Abdominal TB, Renal TB, Lymph Nodes, Pericarditis and Bones and Joints) and genetic disorders, iatrogenic factors, including improper use of antibiotics and non-steroidal anti-inflammatory drugs (NSAIDS) or glucocorticoids, undernutrition, including tobacco exposure and pollution aggravate this condition, weakening the host's immune response (98).

In pediatrics, evaluating a child for TB relies on the following:

- Clinical assessment,
- Thorough medical history, including contact with someone who had TB, previous TB treatment, BCG vaccination, and signs and symptoms consistent with TB;
- Clinical examination, including growth assessment;
- HIV testing if the status is unknown;
- TBI analysis (TST or IGRA) may be obtained by Sputum Induction (99-105).
- Radiological investigations, and;
- Bacteriological measurements, including those relevant to presumed, Extra-pulmonary tuberculosis (EPTB)

2.10.1. First Line Medications are

Rifampin, Isoniazid, Pyrazinamide, and Ethambutol. (RIPE).

2.10.2. Second Line Medications are

Kanamycin (discontinued use in the USA), Streptomycin, Capreomycin, Amikacin, Levofloxacin, Moxifloxacin, and Gatifloxacin.

There are several short and effective tuberculosis preventive treatment (TPT) regimens recommended by the WHO, as of July 2024 (RIPE), although there are special considerations for Children Living with HIV (CLHIV);

- Six or nine months of isoniazid daily;
- Three months of weekly isoniazid plus rifapentine;

- Three months of isoniazid plus rifampicin daily;
- One month of daily isoniazid plus rifapentine; and
- Four months of daily rifampicin (106)

Regarding newborns, protection is achieved through TPT. TPT treats newborns who are uninfected and unvaccinated, but have been exposed to the tuberculosis bacillus. Anti-tuberculosis therapy is administered for a duration of 3 months. Subsequently, a (TST) or (IGRA) is utilized to ascertain the child's infection status. If the result is positive, treatment continues; if negative, the therapy is halted, and the child receives a BCG vaccination. The duration of treatment depends on the drug used for prevention (107-108).

Obstacles in combating multi-drug-resistant tuberculosis in pediatric patients include monitoring for toxicity, especially where HIV infection is common. Pediatric patients with strong family support demonstrate the best treatment adherence (109). Motivation by healthcare workers during a study to follow drug schedules was found statistically significant to treatment compliance with a P-value of 0.0422 (110,1).

Pediatric multidrug-resistant tuberculosis (MDR-TB) remains a significant global problem, and there are numerous barriers preventing children with MDR-TB from being identified, confirmed with microbiologic tests, and treated with a safe, practical, and effective regimen. The treatment of MDR-TB requires medications for a long duration (up to 20–24 months) with less effective and toxic second-line drugs and has unfavorable outcomes (111,20). For children diagnosed with MDR-TB, treatment regimens have traditionally been long and utilize multiple drugs associated with significant side effects, particularly injectable agents. Several new or repurposed drugs including bedaquiline, delamanid, clofazimine and linezolid now allow most treatment regimens to be shorter and totally by an oral route (111-112),20,4). MDR-TB Medications are Bedaquiline, Delamanid, Linezolid, and Pretomanid (113,19).

2.11. Key Messages/Points

- TB is often diagnosed by the combination of a positive TST or IGRA, abnormal chest x-ray and a history of contact with a case of infectious TB, in addition to compatible clinical signs or symptoms;
- Targeted testing for (LTBI) is recommended according to risk of infection and progression to disease;
- Patients for whom therapy of LTBI is recommended should be informed of the risk of treatment and its side effects. Clear plans of action should be in place for monitoring toxicity; and
- The principal recommended regimen for LTBI is 9 months of INH (113-115).

2.12. Pharmacokinetics (PK) and Safety Data Gaps

PK plays a very important role for the selection of optimal dose of a drug. Significant PK and safety data gaps in children for antituberculosis drugs remain, and further research is necessary to determine optimal drug doses and regimens and to ensure safe and effective levels of drug exposure in children (116). One way to achieve this goal is to conduct robust PK studies across the age groups (including neonates) so that the 'right dose' for antituberculosis drugs can be determined both in adults and children (117-119). A robust PK study indicates that the blood sampling scheme is long enough to correctly characterize the half-life and area under the curve (AUC) or clearance.

Several important points regarding robust PK studies and optimal dosing of antituberculosis drugs were pointed out by Mahmood (120-121) and were as follows:

- WHO recommends that the dose of antituberculosis medicines both in adults and children should be based on PK studies. This is in the right direction but it is not clear whether these recommended doses are based on clinical trials, pediatric PK studies, or extrapolated from adult doses on a per kg body weight basis.
- The pediatric recommended doses by the WHO may be due to the unavailability of appropriate pediatric formulations, which limits the ability to administer more precise doses in children.
- The WHO and FDA recommend the dosing for antituberculosis drugs based on weight bands. These weight bands are very wide especially in the younger children. The weight bands should be revaluated because there may be concerns with safety and efficacy.
- Pediatric dosing selection based on the matching the adult exposure with pediatric exposure may and may not be always applicable.
- TB is common to all ages therefore; clinical trials should include very young children after safety and efficacy of an antituberculosis drug is established in adults. It should be recognized that preterm and term neonates as well as neonates with extremely low birth weight or very low birth weight may have entirely different exposure to antituberculosis medicines than the older children and adults.

- Population PK studies are conducted with sparse sampling across the age groups and is a very suitable approach for determining the PK in the neonates. However, theoretical allometric exponents such as 0.75 and 1.0 for clearance and volume distribution, respectively, should be avoided especially, when young children data are in population PK studies. The exponents of allometry are data dependent and one should not assume that the exponents of allometry will not change with the data and always remain the same irrespective of data.

Additionally, Mahmood discussed a comparison of different methods for the first-in-pediatric dose selection, the author recommended conducting an ethical pediatric clinical trial, it is important to optimize pediatric dose as accurately as possible. The study provided an estimate of first-in-pediatric dose by simple methods to initiate pediatric clinical trials utilizing the Salisbury rule which is based on body weight and is very simple and works fairly well in children >30 kg body weight and can be even used in clinical settings (122). Mahmood also conducted research in Dosing in children: a critical review of the pharmacokinetic allometric scaling and modelling approaches in pediatric drug development and clinical settings. During any pediatric study design it should be recognized that children are not small adults. Theoretically, dose selection in pediatric drug development or clinical settings can be done by using either body weight or the clearance of a drug. This review took a critical look at these approaches and highlights the application and limitations of these proposed methods (123). Tegenge and Mahmood, conducted a study in Prediction of clearance in neonates and adolescents, a comparative study between allometric scaling and physiologically based pharmacokinetic modeling. The objective of this study was to compare the predictive performance of an allometric model with that of a physiologically based pharmacokinetic (PBPK) model to predict clearance or area under the concentration-time curve (AUC) of drugs in subjects from neonates to adolescents. This study indicated that the predictive power of PBPK and allometric models was essentially similar for the prediction of clearance or AUC in pediatric subjects ranging from neonates to adolescents (124-125).

2.13. Risk factors

Because of their age, infants and young children with LTB are at higher risk for developing ATB if they

- Live with family members or other adults who have risk factors for TB;
- Born in or frequently travel to countries where TB is common, including some countries in Asia, Africa, and Latin America;
- Live or used to live in large group settings where TB is more common, such as homeless shelters, prisons, or jails;
- Recently spent time with someone who has active TB disease;
- Have a weaker immune system because of certain medications or health conditions such as diabetes, cancer, and HIV; (126-127,51)
- TB typically affects the lungs of a person (i.e., pulmonary TB) but can also spread to other parts of the body (i.e., extrapulmonary TB);
- TB is prevalent in low- and middle-income countries, as the disease is associated with poverty, poor sanitation or hygiene practices and being easily transmissible from person to person. However, high income countries, including Canada, still report cases of TB, and it is considered an important public health matter; (112,107,51)
- Shorter regimens help patient's complete treatment faster. Healthcare providers can choose the appropriate TB treatment regimen based on drug-susceptibility results, coexisting medical conditions (e.g., HIV, metabolic syndrome), and potential for drug-drug interactions (128).

Static tuberculosis case detection and increasing TB drug resistance are in part the result of deteriorating laboratory services, and a lack of new TB diagnostic tools. Diagnostic innovation with research prompted by concerns about the global spread of drug resistance and transmission of human immunodeficiency virus (HIV) have been noted (102,76).

3. Conclusion

Infants may develop congenital tuberculosis from an infectious mother or, most commonly, they may acquire postnatal disease by contact with an infectious adult source. Important epidemiologic, pathogenetic, and clinical data regarding the management of infantile disease are reviewed. Diagnostic evaluation includes tuberculin skin tests, chest radiography and other imaging studies, smears and cultures, examination of the cerebrospinal fluid, and polymerase chain reaction, as well as the more recent interferon-gamma assay (129-134,29.16).

Regarding pediatric TB, most children needing evaluation for TB disease are not identified by health services, and 90% of the 205,000 children estimated to die from TB each year are never diagnosed or treated (135,73). Data suggest that as many as 20 million children are exposed to TB annually, and 7.5 million child household contacts should be evaluated

each year. Yet most of these children receive no screening or TB infection treatment. Global data show that fewer than 23% of children under the age of five years who were eligible for TB infection treatment (preventive therapy) received this basic intervention in 2017 (136-137,128,27).

Since children are a vulnerable population to TB that has been systematically overlooked in past TB control efforts, they should be prioritized when it comes to TB prevention (138,27). In order for this to happen, multiple challenges must be addressed, including finding children who have been exposed to TB, detecting TB infection in these children (or using close exposure as a proxy for infection), identifying those at highest risk of disease progression, implementing treatment of TB infection, and galvanizing multiple stakeholders to support success.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

References

[1] Katirayi, L., Masaba, R., Tchounga, B., et al. 'We did not even know it was tuberculosis': a qualitative evaluation of integrating tuberculosis services into paediatric entry points in the CaP-TB programme in Cameroon and Kenya. BMJ Public Health 2 (2024).

[2] World Health Organization. Global tuberculosis report 2024 (World Health Organization, 2024).

[3] World Health Organization. WHO consolidated guidelines on tuberculosis. Module 6: tuberculosis and comorbidities (World Health Organization, 2024).

[4] Verkuijl, S. Updated WHO guidance on the management of tuberculosis in children and adolescents. (2022).

[5] Rodriguez-Morales, A.J., Ntoumi, F., Abbara, A., et al. World tuberculosis day 2023-Reflections on the spread of drug-resistant tuberculosis by travellers and reducing risk in forcibly displaced populations. Travel Medicine and Infectious Disease 53 (2023).

[6] Nelson, L.J. and Wells, C.D. Global epidemiology of childhood tuberculosis [Childhood TB]. The International journal of Tuberculosis and lung Disease 8, 636–647 (2004).

[7] Furin, J. Advances in the diagnosis, treatment, and prevention of tuberculosis in children. Expert review of respiratory medicine 13, 301–311 (2019).

[8] Figueroa-Damián, R. and Arredondo-García, J.L. Neonatal outcome of children born to women with tuberculosis. Arch. Med. Res. 32, 66–69 (2001).

[9] Seddon J. A., Shingadia. D., Epidemiology and disease burden of tuberculosis in children: a global perspective. Infection and Drug Resistance 7, 153–165 (2014).

[10] Lamb, G.S. and Starke, J.R. Tuberculosis in infants and children. Tuberculosis and Nontuberculous Mycobacterial Infections, 541–569 (2017).

[11] Lewis, D.B., Weitkamp, J. and Levy, O. Developmental immunology and role of host defenses in fetal and neonatal susceptibility to infection. In Remington and Klein's Infectious Diseases of the Fetus and Newborn Infant 73–159. e14 (Elsevier, 2025).

[12] Siddiqui, M.K., Khan, S., Bhutia, R., et al. Prevalence and factors associated with tuberculosis infection (TBI) among residents of a monastery situated in a high-TB burden area: A cross-sectional study, Sikkim, India. PLoS One 20, e0333583 (2025).

[13] Bisero, E. Diagnosis of Tuberculosis in Pediatric Patients. Current State of Knowledge. (2020).

[14] Palmer, A.C., Bedsaul-Fryer, J.R. and Stephensen, C.B. Interactions of Nutrition and Infection: The Role of Micronutrient Deficiencies in the Immune Response to Pathogens and Implications for Child Health. Annu. Rev. Nutr. 44 (2024).

[15] Goletti, D., Al-Abri, S. M., Giovanni B., et al. World Tuberculosis Day 2023 theme "Yes! We Can End TB!". International Journal of Infectious Diseases 130, S1–S3 (2023).

[16] Gupta, A., Chandra, E., Anand, S., et al. Latent tuberculosis diagnostics: current scenario and review. Monaldi Archives for Chest Disease (2024).

[17] Choi, S., Oh, C., Lee, J., et al. Contact Investigations With a Single Tuberculin Skin Test on Infants Exposed to Tuberculosis in a Postpartum Care Center During the Neonatal Period. J. Korean Med. Sci. 38 (2023).

[18] Robsky, K.O., Chaisson, L. H., Naufal, F., et al. Number needed to screen for tuberculosis disease among children: a systematic review. Pediatrics 151, e2022059189 (2023).

[19] Duong, V.T., Skwarczynski, M. and Toth, I. Towards the development of subunit vaccines against tuberculosis: The key role of adjuvant. Tuberculosis 139, 102307 (2023).

[20] The World Health Organization, (Updated WHO guidance on the management of tuberculosis in children and adolescents. (2022).

[21] Kwon, K.W., Choi, H., Choi, H., et al. Immunogenicity and protective efficacy of RipA, a peptidoglycan hydrolase, against Mycobacterium tuberculosis Beijing outbreak strains. Vaccine 42, 1941–1952 (2024).

[22] Ferrari, S., Zanoni, M., Mangeli, A., et al. Bacteriological culture and direct PCR for detecting the Mycobacterium tuberculosis complex in the Italian eradication campaign: a decade of experience at the National Reference Laboratory. J. Appl. Microbiol. 135, lxae064 (2024).

[23] Hamada, Y., et al. Are mRNA based transcriptomic signatures ready for diagnosing tuberculosis in the clinic? - A review of evidence and the technological landscape. eBioMedicine 82 (2022).

[24] Mackay, I.M., Arden, K.E. and Nitsche, A. Real-time PCR in virology. Nucleic Acids Res. 30, 1292–1305 (2002).

[25] Ssengooba, W., et al. Performance evaluation of Truenat MTB and Truenat MTB-RIF DX assays in comparison to gene XPERT MTB/RIF ultra for the diagnosis of pulmonary tuberculosis in Uganda. BMC Infectious Diseases 24, 190 (2024).

[26] Wang, S., Forsman, L. D., Xu, C., et al. Second-line antituberculosis drug exposure thresholds predictive of adverse events in multidrug-resistant tuberculosis treatment. International Journal of Infectious Diseases 140, 62–69 (2024).

[27] Shingadia, D. and Novelli, V. Diagnosis and treatment of tuberculosis in children. The Lancet infectious diseases 3, 624–632 (2003).

[28] Mehta, P.K., Dahiya, B., Sharma, S., et al. Immuno-PCR, a new technique for the serodiagnosis of tuberculosis. J. Microbiol. Methods 139, 218–229 (2017).

[29] World Health Organization. WHO operational handbook on tuberculosis. Module 3: diagnosis-rapid diagnostics for tuberculosis detection (World Health Organization, 2024).

[30] Gupta, A., Hughes, M.D., Cruz, J.L., et al. Adverse Pregnancy Outcomes Among Women with Human Immunodeficiency Virus Taking Isoniazid Preventive Therapy During the First Trimester. Clinical Infectious Diseases 78, 667–673 (2024).

[31] Thimmappa, D., Mallikarjuna, M.N. and Vijayakumar, A. Breast tuberculosis. Indian J. Surg. 77, 1378–1384 (2015).

[32] Sinha, R. and Rahul. Breast tuberculosis. Indian Journal of Tuberculosis 66, 6–11 (2019).

[33] Mi, J., Wu, X. and Liang, J. The advances in adjuvant therapy for tuberculosis with immunoregulatory compounds. Frontiers in Microbiology 15, 1380848 (2024).

[34] Jones, N.T., Abadie, R., Keller, C.L., et al. Treatment and Toxicity Considerations in Tuberculosis: A Narrative Review. Cureus 16 (2024).

[35] Singh, L., Bangalee, V., Ramasir, S. and Mathibe, L.J. Adverse effects associated with Kanamycin, Amikacin, Capreomycin and Bedaquiline-a VigiAccessTM study. African Health Sciences 24, 62–70 (2024).

[36] Mane, S.S. and Shrotriya, P. Current epidemiology of pediatric tuberculosis. Indian J. Pediatr. 91, 711–716 (2024).

[37] Gennaro, M.L. and Doherty, T.M. Immunodiagnosis of tuberculosis: new questions, new tools conference 2008. 4, I1 (2010).

[38] Dheda, K., Schwander, S.K., Zhu, B., van Zyl-Smit, R.N. and Zhang, Y. The immunology of tuberculosis: from bench to bedside. Respirology 15, 433–450 (2010).

[39] World Health Organization. Third WHO consultation on the translation of tuberculosis research into global policy guidelines: meeting report, 4 April 2023 (World Health Organization, 2023).

[40] Ray, S., Talukdar, A., Kundu, S., Khanra, D. and Sonthalia, N. Diagnosis and management of miliary tuberculosis: current state and future perspectives. Therapeutics and clinical risk management, 9–26 (2013).

[41] Sharma, S.K., Mohan, A. and Sharma, A. Challenges in the diagnosis and treatment of miliary tuberculosis. Indian J. Med. Res. 135, 703–730 (2012).

[42] Sharma, S.K. and Mohan, A. Miliary tuberculosis. Tuberculosis and nontuberculous mycobacterial infections, 415–435 (2021).

[43] Sharma, S.K., Kohli, M., Yadav, Raj N., et al. Evaluating the diagnostic accuracy of Xpert MTB/RIF assay in pulmonary tuberculosis. PloS one 10, e0141011 (2015).

[44] Walters, E., Goussard, P., Bosch, C., et al. GeneXpert MTB/RIF on bronchoalveolar lavage samples in children with suspected complicated intrathoracic tuberculosis: a pilot study. Pediatr. Pulmonol. 49, 1133–1137 (2014).

[45] Yeh, J., Lin, S. and Lin, W. Congenital tuberculosis in a neonate: a case report and literature review. Frontiers in Pediatrics 7, 255 (2019).

[46] Mittal, H., Das, S. and Faridi, M. Management of newborn infant born to mother suffering from tuberculosis: current recommendations and gaps in knowledge. Indian J. Med. Res. 140, 32 (2014).

[47] Subramaniam, S., Kanhere, M., Shephard, L., et al. A case of severe Mycobacterium thermoresistibile pneumonia. Respirology Case Reports 12, e01308 (2024).

[48] World Health Organization, (High TB burden country profiles (2024).

[49] Wei, X., Xie, M., Wu, S. et al. The clinical features and prognostic factors of miliary tuberculosis in a high tuberculosis burden area. Ann. Med. 56, 2356647 (2024).

[50] Jenkins, H.E. and Starke, J. Revealing Gaps in Our Understanding of Finding Children With TB and Our Ability to Inform Policy. Pediatrics 151, e2022059849 (2023).

[51] Moore, B.K., Graham, S.M., Nandakumar, S., et al. Pediatric Tuberculosis: A Review of Evidence-Based Best Practices for Clinicians and Health Care Providers. Pathogens 13, 467 (2024).

[52] Yong, E. Genes from Chagas parasite can transfer to humans and be passed on to children. National Geographic-Phenomena: Not Exactly Rocket Science (2010).

[53] Tchakounte Youngui, B., Tchounga, B.K., Graham, S.M. et al. M. Tuberculosis infection in children and adolescents. Pathogens 11, 1512 (2022).

[54] Gutiérrez-González, L.H., Luis H., Juárez, E., et al. Immunological aspects of diagnosis and management of childhood tuberculosis. Infection and Drug Resistance, 929–946 (2021).

[55] The World Health Organization, (. Framework for the evaluation of new tests for tuberculosis infection. https://www.who.int/publications/i/item/9789240007185 2024 (2024).

[56] Kunnath-Velayudhan, S. and Gennaro, M.L. Immunodiagnosis of tuberculosis: a dynamic view of biomarker discovery. Clin. Microbiol. Rev. 24, 792–805 (2011).

[57] Chegou, N.N., Heyckendorf, J., Walzl, G., et al. Beyond the IFN-γ horizon: biomarkers for immunodiagnosis of infection with Mycobacterium tuberculosis. European Respiratory Journal 43, 1472–1486 (2014).

[58] Cao, T., Liu, X., Yang, C., M et al. Multidrug-resistant tuberculosis in middle ear: A case report. Journal of Clinical Tuberculosis and Other Mycobacterial Diseases 31, 100355 (2023).

[59] Tesini, B.L. Perinatal Tuberculosis (TB) - Pediatrics. Merck Manuals Professional Edition 2023 (2022).

[60] Sundaram, K. and Vajravelu, L.K. Tuberculosis and its clinical consequences on Women's health. Indian Journal of Tuberculosis 71, 195–203 (2024).

[61] Hasan, N., Nourse, C., Schaaf, H.S., et al. Management of the infant born to a mother with tuberculosis: a systematic review and consensus practice guideline. The Lancet Child and Adolescent Health (2024).

[62] Starshinova, A., Kudryavtsev, I. V., Rubinstein, A., et al. BCG vaccination: historical role, modern applications, and future perspectives in tuberculosis and beyond. Frontiers in Pediatrics 13, 1603732 (2025).

[63] Botaro, M.H., e Silva, J.M., Jamra, S.R.A., et al. BCG vaccination in children with severe combined immunodeficiency in a tertiary center: evaluation of complications and risks. J. Pediatr. 101, 224–230 (2025).

[64] Kaufmann, S.H. The Paediatric BCG Vaccine Century: From Historical Success to Future Innovations. Acta Paediatrica (2025).

[65] Davoli, C., Rossi, C., Ciccarone, A., et al. Can 6-month long regimens become the standardized treatment for MDR-TB globally? International Journal of Infectious Disease, 108065 (2025).

[66] Hughes, J. Pharmacokinetics and safety of group A and B Anti-Tuberculosis drugs used in treatment of Rifampicin-Resistant tuberculosis during pregnancy and Post-Partum: A narrative review. Pathogens 12, 1385 (2023).

[67] Mokhele, I., Jinga, N., Berhanu, R., et al. Treatment and pregnancy outcomes of pregnant women exposed to second-line anti-tuberculosis drugs in South Africa. BMC pregnancy and childbirth 21, 453 (2021).

[68] Starshinova, A., Belyaeva, E., Irtyuga, O., et al. Tuberculosis in Pregnant Women After COVID-19: Features of Prevention, Diagnosis, and Treatment (Narrative Review). Journal of Clinical Medicine 14, 5681 (2025).

[69] Maheshwari, P., Dixit, R., Gupta, A. et al. Adverse Drug Reactions in the Treatment of Drug-Resistant Tuberculosis: A Narrative Review. UAPM Journal of Respiratory Diseases and Allied Sciences 2, 33–43 (2025).

[70] Yerramsetti, S., Cohen, T., Atun, R. et al. Global estimates of paediatric tuberculosis incidence in 2013–19: a mathematical modelling analysis. The Lancet Global Health 10, e207–e215 (2022).

[71] Li, X., Qiu, J., Ma, Y. et al.. Reactivation of latent Mycobacterium tuberculosis infection with different outcomes after in vitro fertilization and embryo transfer: two case reports. Gynecology and Pelvic Medicine 6 (2023).

[72] Britton, P., Perez-Velez, C.M. and Marais, B.J. Diagnosis, treatment and prevention of tuberculosis in children. New South Wales Public Health Bulletin 24, 15–21 (2013).

[73] Reuter, A., Seddon, J.A., Marais, B.J. et al. Preventing tuberculosis in children: A global health emergency. Paediatric respiratory reviews 36, 44–51 (2020).

[74] Ayieko, J., Abuogi, L., Simchowitz, B., et al. Efficacy of isoniazid prophylactic therapy in prevention of tuberculosis in children: a meta–analysis. BMC infectious diseases 14, 1–10 (2014).

[75] Finlayson, H., Lishman, J. and Palmer, M. What's new in childhood tuberculosis. Curr. Opin. Pediatr. 35, 166–175 (2023).

[76] Weyer, K., Carai, S. and Nunn, P. Viewpoint TB diagnostics: what does the world really need? J. Infect. Dis. 204, S1196–S1202 (2011).

[77] Thomas, T.A. Tuberculosis in Children. Pediatr. Clin. North Am. 64, 893–909 (2017).

[78] Wasilewski, T., Kamysz, W. and Gębicki, J. AI-Assisted Detection of Biomarkers by Sensors and Biosensors for Early Diagnosis and Monitoring. Biosensors 14 (2024).

[79] Kamra, E., Prasad, T., Rais, A., et al. Diagnosis of genitourinary tuberculosis: detection of mycobacterial lipoarabinomannan and MPT-64 biomarkers within urine extracellular vesicles by nano-based immuno-PCR assay. Scientific Reports 13, 11560 (2023).

[80] Rao, P.S., Modi, N., Nguyen, N., et al. Alternative Methods for Therapeutic Drug Monitoring and Dose Adjustment of Tuberculosis Treatment in Clinical Settings: A Systematic Review. Clin. Pharmacokinet. 62, 375–398 (2023).

[81] Huynh, J., Abo, Y., du Preez, K., et al. Tuberculous meningitis in children: reducing the burden of death and disability. Pathogens 11, 38 (2021).

[82] Della Bella, C., Motisi, M.A., Venturini, E., et al. Performance evaluation of the LIOFeron® TB/LTBI IGRA for screening of paediatric LTBI and tuberculosis. Eur. J. Pediatr. 184, 147 (2025).

[83] Pace, D., Pellegrino, R., Dalpiaz, I., et al. GeneXpert MTB/RIF Ultra in Pediatric Tuberculosis: How Disease Characteristics Modify Test Performances. Current Pediatric Reviews (2025).

[84] Fumagalli, G., Riccardi, N., Catalano, G., et al. TB Anywhere, TB Everywhere. The First Case of pre-Extensively Drug Resistant Tuberculosis Treated with BPaL in Italy: Challenges and Opportunities for Transborder Collaboration. Microbial Drug Resistance 31, 12–15 (2025).

[85] Rizzi, A., Nucera, E., Mazzucco, W., et al. An interoperable web-based platform to support health surveillance against latent tuberculosis infection in health care workers and students: The evolution of CROSSWORD study protocol. PloS one 20, e0319568 (2025).

[86] Stroffolini, G., Lupia, T., Gaviraghi, A., et al. Prescription habits and drugs accessibility for the treatment of non-tuberculous mycobacteria infections in Italy: a multicentric survey from the IRENE study group. Infection 53, 383–392 (2025).

[87] Stabile, I., Chard, T., Grudzinskas, G., Maternal Diseases in Pregnancy. Clinical Obstetrics and Gynaecology , 67–105 (2000).

[88] Mofenson, L.M., Brady, M.T., Danner, S.P., et al. Guidelines for the prevention and treatment of opportunistic infections among HIV-exposed and HIV-infected children: recommendations from CDC, the National Institutes of Health, the HIV Medicine Association of the Infectious Diseases Society of America, the Pediatric Infectious Diseases Society, and the American Academy of Pediatrics. MMWR Recomm Rep 58, 1–166 (2009).

[89] World Health Organization. Making pregnancy safer: assessment tool for the quality of hospital care for mothers and newborn babies (No. EUR/09/5084627). Copenhagen: WHO Regional Office for Europe. Making pregnancy safer: assessment tool for the quality of hospital care for mothers and newborn babies (2009).

[90] World Health Organization. Assessment tool for hospital care: improving the quality of care for reproductive, maternal, neonatal, child and adolescent health in South-East Asia. (2016).

[91] Dowling, J.M. and Yap, C.F. Communicable Diseases in Developing Countries: Stopping the Global Epidemics of HIV/AIDS, Tuberculosis, Malaria and Diarrhea (Springer, 2014).

[92] Thadchanamoorthy, V., Dayasiri, K. and Arulpragasam, A.N. Management of Children with COVID-19.

[93] Rafiq, N.B. Normal pregnancy, labor, and delivery. In Family Medicine: Principles and Practice 137–148 (Springer, 2022).

[94] Me, V.B.D.L. Perinatal and Maternal Medicine. Book of, 204.

[95] Iles, A. Rapid point-of-care testing solutions to meet clinical needs Rapid point-of-care testing solutions to meet clinical needs (2023).

[96] Huynh, J. Improving The Diagnosis And Prognosis Of Tuberculous Meningitis In Children. Open Research Online - ORO (2024).

[97] Ma, W., Wang, L., Zhao, D., et al. Analysis of T-lymphocyte subsets and risk factors in children with tuberculosis. Tuberculosis 146, 102496 (2024).

[98] Cardinale, F., La Torre, F., Tricarico, L.Get al. Why do some children get sick with recurrent respiratory infections? Current Pediatric Reviews 20, 203–215 (2024).

[99] Araújo, L., Moreira, A., Palmares, C., et al.. 8 Induced Sputum in Children: Success Determinants, Safety, and Cell Profiles. Journal of Investigational Allergology and Clinical Immunology 21, 216 (2011).

[100] Chanez, P., Holz, O., Ind, P.W., et al. Sputum induction. European Respiratory Journal 20, 3s–8s (2002).

[101] Guiot, J., Demarche, S., Henket, M., et al. Methodology for sputum induction and laboratory processing. Journal of visualized experiments: JoVE (2017).

[102] Mussaffi, H., Fireman, E.M., Mei-Zahav, M., et al. Induced Sputum in the Very Young: A New Key to Infection and Inflammation. Chest 133, 176–182 (2008).

[103] Hill, K., Burgen, O., Dautry, M., et al. ECFS CTN SOP sputum induction for expectorating older children and adults. (2024).

[104] Pizzichini, M., Leigh, R., Djukanović, R. et al. Safety of sputum induction. European Respiratory Journal 20, 9s–18s (2002).

[105] Schultz, A., Balaguruswamy, S., Dentice, R., et al. Thoracic Society of Australia and New Zealand position statement: The safe clinical use of sputum induction for bio-sampling of the lower airways in children and adults. Respirology 29, 372–378 (2024).

[106] Shah, P., Pol, S., Prabhakaran, E., et al. Utility of GeneXpert in Diagnosis of Pediatric Tuberculosis and Detection of Rifampicin Resistance. Perspectives 12, 48 (2024).

[107] Chiang, S.S., Roche, S; Contreras, C., et al. Barriers to the treatment of childhood tuberculous infection and tuberculosis disease: a qualitative study. The International Journal of Tuberculosis and Lung Disease 21, 154–160 (2017).

[108] TannousTahan, T., de Oliveira Rossoni, A. M., Lugarini, G., et al. Tuberculosis preventive treatment in newborns. J. Pediatr. (2024).

[109] Chiang, S.S., Tanzer, J.R., Starke, J.R., et al. Identifying adolescents at risk for suboptimal adherence to tuberculosis treatment: A prospective cohort study. PLOS Global Public Health 4, e0002918 (2024).

[110] Zaidi, I., Sarma, P.S., Khayyam, K.U., et al. Factors associated with treatment adherence among pulmonary tuberculosis patients in New Delhi. Indian Journal of Tuberculosis 71, S52–S58 (2024).

[111] Jang, J.G. and Chung, J.H. Diagnosis and treatment of multidrug-resistant tuberculosis. Yeungnam University journal of medicine 37, 277–285 (2020).

[112] Brett, K., Dulong, C. and Severn, M. Treatment of tuberculosis: a review of guidelines. (2020).

[113] Padda, I.S. and Muralidhara Reddy, K. Antitubercular Medications. In StatPearls (StatPearls Publishing, Treasure Island (FL), 2023).

[114] World Health Organization. Best practices in child and adolescent tuberculosis care (World Health Organization, 2018).

[115] Heymann, S.J., Brewer, T.F., Wilson, M.E., et al. Pediatric tuberculosis: what needs to be done to decrease morbidity and mortality. Pediatrics 106, e1 (2000).

[116] Zou, Y., Nedelman, J., Karlsson, M.O. et al. A Novel Approach to Evaluating the Design of Pediatric Pharmacokinetic Studies Focused on Accurate Dose Selection. Clin. Pharmacokinet., 1–9 (2025).

[117] Dudnyk, A., Lutchmun, W., Duarte, R., et al. The importance of getting the dose right in the treatment of tuberculosis. Breathe 21 (2025).

[118] Svensson, E.M., Yngman, G., Denti, P., et al. Evidence-based design of fixed-dose combinations: principles and application to pediatric anti-tuberculosis therapy. Clin. Pharmacokinet. 57, 591–599 (2018).

[119] Cella, M., Knibbe, C., Danhof, M. et al. What is the right dose for children? Br. J. Clin. Pharmacol. 70, 597 (2010).

[120] Mahmood, I. Two simple methods to predict Pediatric Dose of Antituberculosis Medicines: Application of Allometry and Salisbury Rule. Journal of Clinical and Translational Research 11, 66–72 (2025).

[121] Mahmood, I. A simple method for the prediction of therapeutic proteins (monoclonal and polyclonal antibodies and non-antibody proteins) for first-in-pediatric dose selection: application of salisbury rule. Antibodies 11, 66 (2022).

[122] Mahmood, I. A comparison of different methods for the first-in-pediatric dose selection. Journal of Clinical and Translational Research 8, 369 (2022).

[123] Mahmood, I. Dosing in children: a critical review of the pharmacokinetic allometric scaling and modelling approaches in paediatric drug development and clinical settings. Clin. Pharmacokinet. 53, 327–346 (2014).

[124] Mahmood, I., Ahmad, T., Mansoor, N. et al. Prediction of clearance in neonates and infants (≤ 3 months of age) for drugs that are glucuronidated: a comparative study between allometric scaling and physiologically based pharmacokinetic modeling. The Journal of Clinical Pharmacology 57, 476–483 (2017).

[125] Mahmood, I. and Tegenge, M.A. A comparative study between allometric scaling and physiologically based pharmacokinetic modeling for the prediction of drug clearance from neonates to adolescents. The Journal of Clinical Pharmacology 59, 189–197 (2019).

[126] Mahmood, I. Prediction of drug clearance in premature and mature neonates, infants, and children≤ 2 years of age: a comparison of the predictive performance of 4 allometric models. The Journal of Clinical Pharmacology 56, 733–739 (2016).

[127] Cruz, A.T. and Starke, J.R. Pediatric tuberculosis. Pediatrics in review 31, 13–26 (2010).

[128] Centers for Disease Control and Prevention, (CDC). Tuberculosis (TB) - Treatment for TB Disease. Centers for Disease Control and Prevention 2023 (2023).

[129] World Health Organization. WHO recommendations on antenatal care for a positive pregnancy experience: screening, diagnosis and treatment of tuberculosis disease in pregnant women. Evidence-to-action brief:

Highlights and key messages from the World Health Organization's 2016 global recommendations (World Health Organization, 2023).

[130] Baral, B., Mamale, K., Gairola, S., et al. Infectious diseases and its global epidemiology. In Nanostructured Drug Delivery Systems in Infectious Disease Treatment 1–24 (Elsevier, 2024).

[131] Khan, F.Y. Review of literature on disseminated tuberculosis with emphasis on the focused diagnostic workup. Journal of Family and community Medicine 26, 83–91 (2019).

[132] Alshoabi, S.A., Almas, K.M., Aldofri, S.A., et al. The diagnostic deceiver: radiological pictorial review of tuberculosis. Diagnostics 12, 306 (2022).

[133] KR, T.R., Nagar, S., Khan, N.,et al. A Detailed Overview of Extra Pulmonary Tuberculosis Pathophysiology and its Diagnostic Methods.

[134] Li, Z., Hu, Y., Wang, W., et al. Integrating pathogen-and host-derived blood biomarkers for enhanced tuberculosis diagnosis: a comprehensive review. Frontiers in Immunology 15, 1438989 (2024).

[135] Rampedi, P.N., Ogunrombi, M.O. and Adeleke, O.A. Leading Paediatric Infectious Diseases—Current Trends, Gaps, and Future Prospects in Oral Pharmacotherapeutic Interventions. Pharmaceutics 16, 712 (2024).

[136] Roy, R.B., Bakeera-Kitaka, S., Chabala, C., et al. Defeating paediatric tuberculous meningitis: applying the WHO "defeating meningitis by 2030: global roadmap". Microorganisms 9, 857 (2021).

[137] Moon, H. and Hur, M. Interferon-gamma release assays for the diagnosis of latent tuberculosis infection: an updated review. Annals of Clinical and Laboratory Science 43, 221–229 (2013).

[138] Verkuijl, S., Sekadde, M. P., Dodd, P. J., et al. Addressing the data gaps on child and adolescent tuberculosis. Pathogens 11, 352 (2022).