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CHAPTER 1

Mycobacterium tuberculosis Infection in Children and Women: Age and Sex Specific Description of Diagnosis, Treatment, Prevention and Disease Management

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Abstract: Tuberculosis (TB), caused predominantly by *Mycobacterium tuberculosis*, remains a major global infectious disease with children and women representing important populations requiring age and sex specific approaches to diagnosis, treatment, and prevention. TB in children is frequently characterized by paucibacillary disease, nonspecific clinical manifestations, difficulties in obtaining appropriate clinical specimens and an increased risk of progression from infection to active disease. Non-tuberculous mycobacteria (NTM), including species such as *M. avium* complex, *M. kansasii*, *M. abscessus*, *M. smegmatis*, *M. chelonae* and *M. fortuitum* are clinically relevant

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environmental mycobacteria that can cause pulmonary and extrapulmonary disease and may mimic tuberculosis, necessitating their consideration in differential diagnosis. In women, tuberculosis may involve the lungs as well as extrapulmonary sites, targeting the female reproductive tract, particularly the fallopian tubes, endometrium, ovaries, cervix and less frequently on other genital structures. Female genital tuberculosis may remain clinically silent or present with menstrual abnormalities, pelvic pain, infertility or adverse reproductive outcomes, making timely diagnosis challenging. This article examines the biological, clinical and public-health challenges associated with *M. tuberculosis* infection in children and women with particular emphasis on diagnostic limitations, treatment complexities, drug-resistant TB and reproductive health consequences. Current microbiological, molecular, radiological and immunological diagnostic approaches are discussed, including their limitations in paucibacillary and extrapulmonary disease. Therapeutic strategies are reviewed with emphasis on age-appropriate dosing, treatment adherence, adverse drug reactions, multidrug-resistant and rifampicin-resistant TB and special considerations during pregnancy and lactation. Preventive strategies, including BCG vaccination, contact investigation, TB preventive treatment, infection-control measures, nutritional support and early detection are considered alongside emerging rapid molecular diagnostics, shorter treatment regimens, newer anti-TB drugs, and digital adherence technologies. An integrated, patient-centred approach addressing biological, reproductive, social, and treatment-related factors is essential for improving outcomes and strengthening TB control among children and women.

Keywords: Pediatric tuberculosis; Female genital tuberculosis; Drug-resistant tuberculosis; Multidrug-resistant tuberculosis; TB diagnosis; Anti-tuberculosis therapy.

A. Introduction

Tuberculosis (TB), caused primarily by *Mycobacterium tuberculosis*, remains a major global infectious disease despite substantial advances in diagnosis, treatment, and prevention. According to the World Health Organization (WHO 2025), an estimated 10.7 million people developed TB in 2024, including approximately 1.2 million children and 3.7 million women, highlighting the importance of age- and sex-specific approaches to TB control. In addition to *M. tuberculosis*, non-tuberculous mycobacteria (NTM) comprise a diverse group of environmental mycobacteria capable of causing pulmonary and extrapulmonary disease. Because NTM infections may clinically and radiologically resemble TB, accurate microbiological identification is essential for appropriate treatment (Flynn & Chan, 2001).

Children are particularly vulnerable to TB because of non-specific clinical manifestations, paucibacillary disease and difficulties in obtaining adequate respiratory specimens. Consequently, diagnosis often requires integration of clinical, epidemiological, radiological and molecular evidence. Young children are at increased risk of severe forms of disease including TB meningitis and disseminated TB. Recent advances in molecular diagnostics, shorter treatment regimens for selected non-severe TB, and newer anti-TB drugs have improved diagnostic and therapeutic options. However, distinguishing *M. tuberculosis* from NTM remains important because detection of mycobacteria does not necessarily confirm TB and treatment strategies differ substantially (Motta *et al.*, 2019).

In women, TB presents additional challenges related to pregnancy, lactation, reproductive health, and female genital tuberculosis (FGTB). FGTB may involve the fallopian tubes, endometrium, ovaries, cervix, and other reproductive tissues and may remain asymptomatic or manifest as menstrual disturbances, chronic pelvic symptoms, infertility, or adverse reproductive outcomes. Pregnancy and the postpartum period introduce further diagnostic and therapeutic complexities because physiological and immunological changes may alter disease presentation and influence maternal and perinatal outcomes. Although NTM infection of the female reproductive tract is uncommon, it should be considered in selected cases where microbiological differentiation may influence treatment decisions (Muefong & Sutherland 2022).

Drug-resistant TB (DR-TB) represents another major challenge. WHO estimated approximately 390,000 incident cases of multidrug or rifampicin-resistant TB (MDR/RR-TB) globally in 2024. Management is particularly complex in children because of age-dependent pharmacokinetics, dosing requirements and limited formulations, while pregnancy and breastfeeding require careful assessment of maternal, fetal and infant safety. The increasing use of all-oral regimens and newer drugs, including bedaquiline and fluoroquinolones in appropriate cases, has expanded treatment options (Hossain *et al.*, 2026).

Effective TB control therefore requires early diagnosis, accurate species identification, drug-susceptibility testing, appropriate treatment, adherence support, contact investigation and TB preventive treatment. Understanding differences in immune maturation, developmental stage, reproductive physiology, pharmacokinetics and clinical presentation is essential for improving TB prevention, diagnosis, treatment, and long-term outcomes in children and women (Shrivas & Singh, 2025).

The central focus of this article is the age- and sex-specific biology, diagnosis, and management of *M. tuberculosis* infection in children and women. It examines how biological and physiological differences influence disease presentation, diagnostic challenges, treatment selection and clinical outcomes. Particular emphasis is placed on pediatric TB, drug-resistant TB, female genital and reproductive tract TB and TB during pregnancy and lactation, while also considering the diagnostic importance of distinguishing *M. tuberculosis* from non-tuberculous mycobacteria. The review further evaluates advances in molecular diagnostics and newer therapeutic approaches and identifies important gaps in evidence and clinical management requiring further investigation.

B. Age and Sex Specific Pathogenesis and Host Immune Response

The pathogenesis of *M. tuberculosis* infection is governed by a complex interaction between the bacillus and host innate and adaptive immune responses. Following inhalation, *M. tuberculosis* is internalized by alveolar macrophages, where pathogen-recognition receptors initiate innate immune responses. Dendritic cells subsequently process mycobacterial antigens and activate T lymphocytes. IL-12, IFN-γ and TNF-α constitute important components of the protective Th1 response, promoting macrophage activation and granuloma formation. Conversely, regulatory and anti-inflammatory pathways involving IL-10, TGF-β and regulatory T cells (Tregs) can modulate inflammation and influence bacterial persistence. The balance between protective immunity and excessive inflammation ultimately determines containment, active disease or dissemination (Zhang *et al.*, 2026).

i. Pediatric Tuberculosis

In children, particularly infants and young children, the developing immune system can influence the progression and severity of TB. Important immunological parameters include $CD4^+$ and $CD8^+$ T-cell populations, Th1/Th2/Th17 responses, IFN-γ, IL-12, TNF-α, IL-6, IL-10 and Treg activity. Compared with adults, young children may demonstrate less mature cell-mediated responses, including reduced or differently regulated production of IFN-γ and other Th1-associated cytokines. This may compromise macrophage activation and granuloma formation, facilitating progression from primary infection to active or disseminated disease.

Th17-associated IL-17 may contribute to recruitment of neutrophils and inflammatory cells, whereas excessive inflammatory responses may contribute to tissue injury. The balance between Th1/Th17-mediated protective immunity and regulatory mechanisms is therefore important in determining disease outcome. In severe pediatric TB, particularly disseminated disease and TB meningitis, altered cytokine profiles and immune dysregulation may accompany extensive

inflammation. Nutritional deficiencies can further influence lymphocyte function, cytokine production and overall antimycobacterial immunity (Mashiach, 2026).

ii. Tuberculosis in Women

In women, the interaction between *M. tuberculosis* and the immune system becomes particularly relevant when infection involves the reproductive tract. Following hematogenous or lymphatic dissemination, bacilli may reach the fallopian tubes, endometrium, ovaries and cervix, where persistent infection induces macrophage activation and granulomatous inflammation. The resulting immune response involves Th1 cells, macrophages, $CD8^+$ T cells, cytokines and chemokines, with IFN-γ and TNF-α contributing to antimycobacterial activity and granuloma formation (Kesharwani *et al.*, 2022).

However, persistent inflammation may lead to caseation, fibrosis, adhesions and tissue remodelling. In the fallopian tubes, chronic inflammation and fibrosis can cause narrowing or obstruction, while endometrial inflammation and subsequent fibrosis may impair endometrial receptivity. These pathological changes can interfere with fertilization, embryo transport and implantation, contributing to infertility, ectopic pregnancy and adverse reproductive outcomes.

Sex hormones can further modulate these immune responses. Estrogen and progesterone influence macrophage function, T-cell differentiation, cytokine production and inflammatory regulation. The immunological environment therefore varies across the menstrual cycle and changes substantially during pregnancy and the postpartum period. Pregnancy is characterized by dynamic regulation of innate and adaptive immunity rather than simple immunosuppression. Changes in Th1/Th2/Th17/Treg balance, cytokines such as IFN-γ, TNF-α, IL-10 and TGF-β, and innate immune-cell activity may influence host control of *M. tuberculosis* (Tzelios *et al.*, 2022).

Thus, immune maturation is a major determinant of disease progression and dissemination in children, whereas in women the interaction between antimycobacterial immunity, reproductive-tissue inflammation and hormonal regulation is particularly important for understanding genital TB and its consequences for fertility and pregnancy.

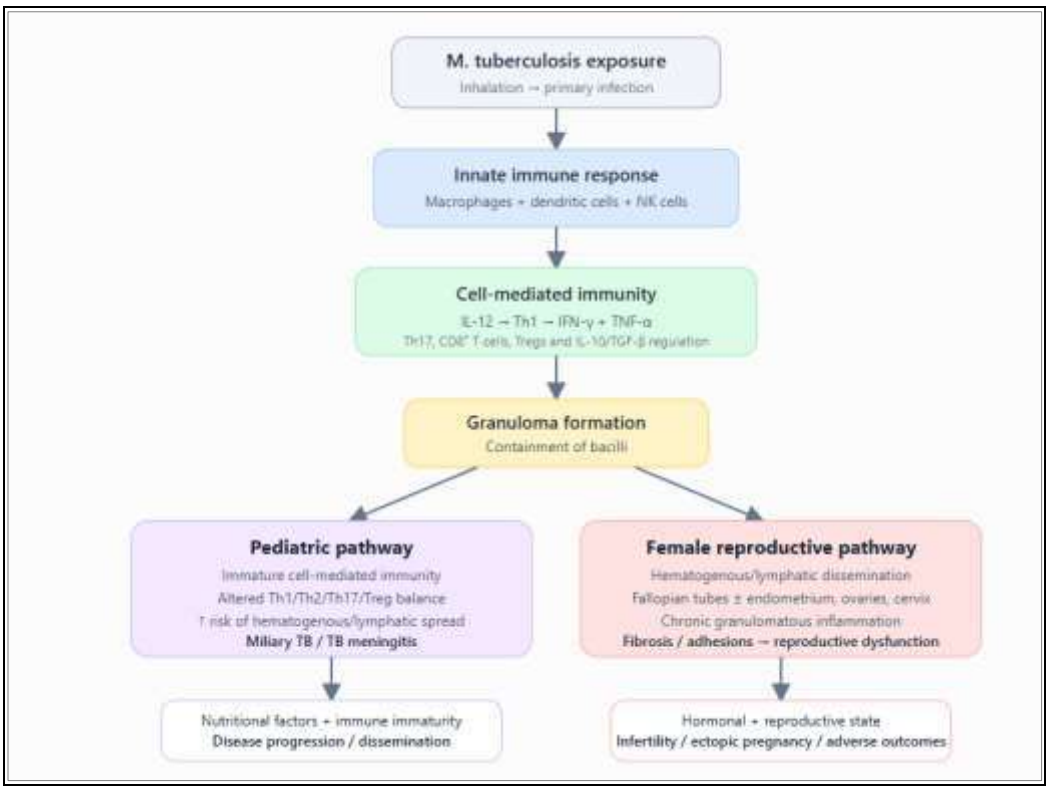

Figure 1: Integrating the age- and sex-specific pathogenesis and immunological parameters of *M. tuberculosis* infection.

C. Biology of the Tuberculous Granuloma in Children and Women

The cellular sequence of tuberculous granuloma formation begins with inhalation of *M. tuberculosis* and uptake of bacilli by alveolar macrophages and dendritic cells. Infected cells release IL-1β, IL-12, TNF-α, and chemokines, initiating recruitment of monocytes, macrophages, neutrophils and lymphocytes. Dendritic cells process and present mycobacterial antigens, activating $CD4^+$ Th1 and $CD8^+$ T cells. Th1 cells produce IFN-γ, which activates macrophages, while TNF-α promotes cellular recruitment and granuloma organization. Recruited macrophages differentiate into epithelioid cells, and some fuse to form multinucleated giant cells, surrounded by lymphocytes and other inflammatory cells. This progressive cellular organization forms the tuberculous granuloma, which may contain bacterial replication and establish latent infection. Failure of effective granuloma organization can lead to caseous necrosis, cavitation, bacterial dissemination, and active TB (Davis & Ramakrishnan, 2009).

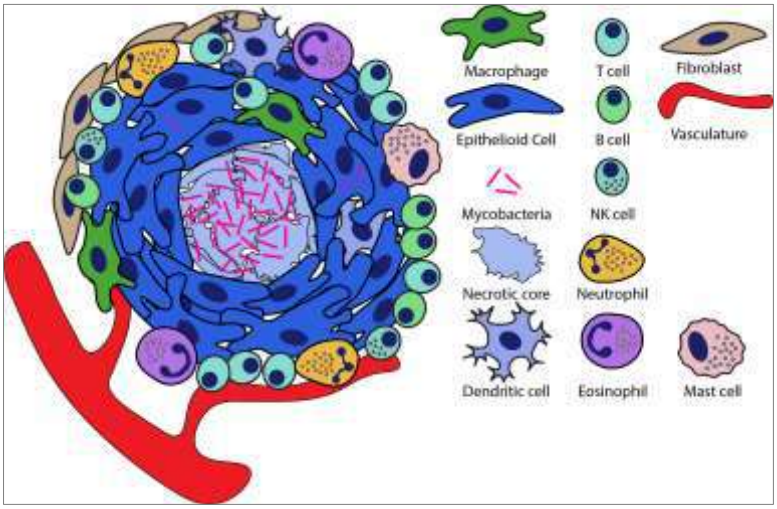

Figure 2: Organization of a granuloma during mycobacterial infection

D. Immunopathogenesis of Pediatric Tuberculosis: From Primary Infection to Disease Progression

Pediatric tuberculosis develops following inhalation of *M. tuberculosis*, which reaches the lungs and is taken up by alveolar macrophages. The ensuing innate and adaptive immune responses involve antigen presentation, T-cell activation, and cytokine-mediated macrophage activation, particularly through IL-12, IFN-γ, and TNF-α. These responses promote granuloma formation and help contain bacterial growth. When immune containment is effective, infection may remain latent; inadequate control can lead to active pulmonary or extrapulmonary disease. In children, especially during early life, the developing immune system may be less efficient at controlling *M. tuberculosis*, contributing to a greater risk of disease progression and dissemination.

i. Infection and Primary Establishment - Pediatric TB begins with inhalation of *M. tuberculosis*, which reaches the alveoli and is engulfed by alveolar macrophages. The bacilli can survive intracellularly by interfering with phagosome–lysosome fusion and may subsequently multiply within macrophages.

ii. Innate Immune Response - Infected macrophages and dendritic cells release cytokines and chemokines that recruit monocytes, neutrophils and lymphocytes to the infection site. Dendritic cells process mycobacterial antigens and initiate the transition from innate to adaptive immunity.

iii. T-Cell-Mediated Immunity - Antigen presentation activates $CD4^+$ T cells, particularly Th1 cells, which produce IFN-γ and TNF-α to enhance macrophage antimicrobial activity and granuloma formation. $CD8^+$ T cells contribute through cytotoxic mechanisms, while Th17 cells promote inflammatory-cell recruitment and mucosal defense.

iv. Developing Immune System - In infants and young children, cell-mediated immunity is still developing, with relatively reduced efficiency of macrophage activation, Th1 responses and cytokine coordination. This can compromise effective containment of *M. tuberculosis* compared with immunologically mature hosts.

v. Granuloma Formation and Containment - Activated macrophages and T cells organize into granulomas that restrict bacterial multiplication. Effective granuloma formation may result in containment and latent infection; inadequate immune containment permits continued bacterial replication and tissue injury.

vi. Disease Progression and Dissemination - When immune control is insufficient, primary infection can progress to progressive pulmonary TB, lymph-node disease or hematogenous dissemination. Young children are particularly susceptible to severe forms such as miliary TB and tuberculous meningitis.

vii. Cytokine and Regulatory Balance - Protective immunity depends on a balance between IFN-γ, TNF-α and IL-12, which support antimycobacterial activity, and regulatory mediators such as IL-10 and Treg responses, which limit excessive inflammation. Disruption of this balance can influence bacterial persistence, granuloma integrity and disease severity (Agullo-Ros *et al.*, 2026).

Overall, pediatric TB reflects a dynamic interaction between *M. tuberculosis* and the developing host immune system. Following inhalation, bacilli are taken up by alveolar macrophages and may persist intracellularly, while antigen presentation activates $CD4^+$ and $CD8^+$ T-cell responses, particularly the Th1 pathway, with IFN-γ and TNF-α promoting macrophage activation and granuloma formation. The outcome depends largely on the balance between mycobacterial persistence and cell-mediated immune containment. In young children, relatively immature immune responses may limit effective bacterial control, increasing the possibility of progression from contained infection to active pulmonary or extrapulmonary disease, including miliary TB and tuberculous meningitis. Thus, age-dependent immunological maturity is an important determinant of the pathogenesis and clinical severity of pediatric TB.

E. Women's TB: Pathogenesis and Immunophysiology

In women, tuberculosis (TB) pathogenesis follows the general sequence of *M. tuberculosis* infection but is influenced by sex hormones, reproductive physiology, pregnancy, nutritional status, and immune regulation. These factors can modify both susceptibility to infection and the clinical expression of disease.

i. Initial infection and pulmonary establishment - *M. tuberculosis* reaches the alveoli through inhaled aerosol droplets. Alveolar macrophages recognize and phagocytose the bacilli, but the organism can inhibit phagosome–lysosome fusion and survive intracellularly. Infected macrophages release cytokines and chemokines that recruit monocytes, dendritic cells and lymphocytes to the site of infection.

ii. Development of adaptive immunity - Dendritic cells transport mycobacterial antigens to draining lymph nodes, where $CD4^+$ T cells, particularly Th1 cells, become activated. IFN-γ enhances macrophage antimicrobial activity, while TNF-α contributes to granuloma formation and maintenance. $CD8^+$ T cells, NK cells and Th17 cells also contribute to antimycobacterial immunity.

iii. Granuloma formation and latent infection - The granuloma represents an organized immune structure that attempts to restrict bacterial multiplication. In effective immune containment, bacilli remain metabolically restricted, producing latent TB infection (LTBI). If immune control weakens, granuloma integrity may deteriorate, permitting bacterial replication and progression to active disease.

iv. Female immunophysiology and TB - Female reproductive physiology can modify TB immunity through estrogen, progesterone and other endocrine signals. Sex hormones interact with immune cells - including macrophages, dendritic cells and T lymphocytes - and can influence cytokine production and inflammatory responses. Estrogen may enhance or suppress different components of immunity depending on its concentration, tissue and physiological state. Thus, Hormonal changes in women can modulate both innate and adaptive immune responses, influencing macrophage activation, T-cell function, and the balance of pro- and anti-inflammatory cytokines. These immunological alterations can affect the ability of the host to contain *M. tuberculosis*, thereby influencing granuloma formation, bacterial persistence, immune-mediated tissue damage, and ultimately the susceptibility, progression, and clinical expression of TB.

v. Pregnancy-associated changes - Pregnancy produces substantial immunological adaptation to support fetal tolerance. Rather than representing a simple global suppression of immunity, pregnancy involves dynamic remodeling of innate and adaptive immune responses, including changes in T-cell activity, cytokine profiles and regulatory mechanisms.

vi. Female genital tuberculosis - Genital TB is usually secondary to infection elsewhere, particularly pulmonary TB, with dissemination through hematogenous or lymphatic routes. The fallopian tubes are commonly involved. Chronic granulomatous inflammation can cause fibrosis, adhesions and tubal obstruction, potentially resulting in infertility, menstrual disturbances, ectopic pregnancy and adverse reproductive outcomes.

The immunological response to tuberculosis in women involves coordinated interactions between innate and adaptive immune components. Following infection, alveolar macrophages engulf *M. tuberculosis* and initiate inflammatory signaling, while dendritic cells process and present mycobacterial antigens to T lymphocytes. Activation of $CD4^+$ Th1 cells promotes secretion of IFN-γ and TNF-α, enhancing macrophage activation and granuloma formation, whereas $CD8^+$ T cells contribute through cytotoxic and antimicrobial functions. Th17 cells support inflammatory-cell recruitment, while regulatory T cells (Tregs) modulate excessive immune activation. Cytokines such as IL-12, IFN-γ and TNF-α promote protective antimycobacterial immunity, whereas IL-10 and other regulatory mediators can limit inflammation but may also reduce effective bacterial clearance. In women, these immune pathways are further influenced by sex hormones and reproductive physiological states, resulting in dynamic changes in immune regulation that may affect TB containment, progression, and tissue pathology (Yengkhom & Weinberg, 2026).

F. Drug-Resistant Tuberculosis in Children and Women

Drug-resistant tuberculosis (DR-TB) in children and women represents an important clinical and public-health concern because drug resistance, host immune characteristics, age, reproductive status and treatment access can influence disease progression and therapeutic outcomes. In children, DR-TB commonly results from exposure to a drug-resistant infectious source rather than the development of resistance during treatment. Limited disease burden, difficulty obtaining adequate microbiological specimens, and challenges in administering weight-adjusted regimens can complicate diagnosis and management. Children may also be particularly vulnerable to severe forms of DR-TB, including disseminated and meningeal disease. In women, DR-TB may intersect with pregnancy, reproductive health, hormonal and immunological changes, requiring careful consideration of drug safety and maternal–fetal effects. Delayed diagnosis, stigma, socioeconomic barriers, and unequal access to healthcare may further influence detection and treatment. Overall,

effective management requires early detection of resistance, appropriate drug-susceptibility testing, individualized age- and weight-appropriate therapy, adherence support, contact investigation, and coordinated reproductive and clinical care, with particular attention to vulnerable pediatric and female populations (WHO, 2025).

G. Prevention and Public-Health Strategies

Prevention and control of tuberculosis (TB) in children and women require an integrated, people-centred approach aligned with the World Health Organization (WHO) End TB Strategy and India's National Tuberculosis Elimination Programme (NTEP). Key interventions include childhood BCG vaccination, systematic screening, early diagnosis, prompt initiation of appropriate treatment, contact investigation, TB preventive treatment (TPT), infection prevention and control, and community-based support. BCG (*Bacille Calmette–Guérin*) vaccine contains a live, attenuated strain of *M. bovis*, a bacterium closely related to *M. tuberculosis*. It is not a weakened strain of *M. tuberculosis*. BCG vaccination remains an important component of childhood TB prevention and is particularly effective in reducing severe forms of TB, including tuberculous meningitis and miliary TB in young children. Following BCG administration, the live attenuated *M. bovis* organisms are taken up by macrophages and dendritic cells, leading to activation of innate immune responses and subsequent antigen presentation. This promotes the activation of $CD4^+$ and $CD8^+$ T lymphocytes, particularly a Th1-type cellular immune response, resulting in the production of cytokines such as IFN-γ, IL-2, and TNF-α. These cytokines enhance macrophage activation and antimicrobial activity, thereby improving the host's ability to contain *M. tuberculosis* following infection and reducing the risk of severe forms of childhood TB, particularly tuberculous meningitis and miliary TB. Systematic identification and screening of household and other close contacts of individuals with pulmonary TB are essential for detecting TB disease and identifying individuals eligible for preventive interventions. WHO recommends TPT for populations at increased risk of progression from TB infection to disease, while NTEP provides programmatic guidance for preventive treatment among eligible household contacts and other high-risk groups after active TB has been excluded. Early and accurate diagnosis, including the use of rapid molecular diagnostic technologies and drug-susceptibility testing, is particularly important in children and other groups in whom conventional diagnosis may be challenging and for the timely detection of drug-resistant TB. In women, TB prevention and care should be integrated with maternal, reproductive, and primary healthcare services to facilitate timely recognition, diagnosis, treatment, and continuity of care during pregnancy and the postpartum period. Addressing undernutrition, socioeconomic vulnerability, stigma, treatment adherence, and barriers to healthcare access, together with

community engagement and patient-centred support, further strengthens TB control. Collectively, these measures contribute to interrupting transmission, preventing progression from TB infection to disease, reducing the emergence and spread of drug resistance, and improving TB-related health outcomes among children and women (Central Tuberculosis Division, Ministry of Health and Family Welfare, GOI, 2025).

H. Emerging Diagnostics and New Therapeutic Strategies

Xpert MTB/RIF and Xpert MTB/RIF Ultra - Xpert MTB/RIF is a rapid, automated molecular nucleic-acid amplification test that simultaneously detects *M. tuberculosis* complex DNA and mutations associated with rifampicin resistance. This is particularly important because rifampicin resistance is a major marker of drug-resistant TB and can indicate the need for further drug-susceptibility testing. Xpert MTB/RIF Ultra, the newer version, has improved analytical sensitivity and is especially useful when the bacterial load is low, as may occur in children and extrapulmonary TB. WHO recommends its use for detecting TB and rifampicin resistance, while emphasizing that a negative molecular result does not completely exclude TB, particularly in children with paucibacillary disease.

For pediatric TB, Xpert Ultra can be performed on appropriately collected respiratory specimens and, depending on the clinical situation and available guidelines, on selected extrapulmonary specimens. Its rapid identification of M. tuberculosis and rifampicin resistance allows earlier initiation of appropriate therapy compared with waiting for conventional culture-based susceptibility results. However, rifampicin resistance detected by Xpert should be followed by additional resistance testing, because treatment selection depends on the complete drug-resistance profile (None *et al.*, 2026).

- **Advances in Immunodiagnostic Techniques for TB in Children**

Diagnosis of tuberculosis (TB) in children remains challenging because children often have paucibacillary disease, making microbiological confirmation difficult. Obtaining adequate respiratory specimens such as sputum is also problematic, particularly in young children. Consequently, conventional acid-fast bacilli (AFB) smear microscopy and culture have relatively low sensitivity, despite culture remaining an important reference method. These limitations can result in delayed or missed diagnosis, particularly in resource-limited, high-burden settings.

To address these challenges, there has been increasing interest in immunodiagnostic and molecular approaches that complement clinical assessment. Current diagnostic tools include nucleic acid amplification tests (NAATs), antigen and antibody detection assays, and interferon-γ

release assays (IGRAs). IGRAs, which measure *M. tuberculosis*-specific T-cell responses, provide evidence of TB infection and are useful particularly when interpreted alongside clinical and epidemiological findings. However, like the tuberculin skin test, they generally cannot reliably distinguish latent TB infection from active disease and may have limitations in young or immunocompromised children.

Emerging host-response biomarkers, including cytokine profiles, transcriptional signatures, immune-cell activation markers, and other blood-based signatures, are being investigated to improve diagnostic accuracy. Nevertheless, no single immunological test currently provides sufficient sensitivity and specificity to independently confirm active childhood TB or reliably differentiate it from other respiratory infections. Therefore, combining clinical evaluation with microbiological, molecular, and immunological evidence remains essential for achieving earlier and more accurate diagnosis of both pulmonary and extrapulmonary TB in children (WHO, 2025).

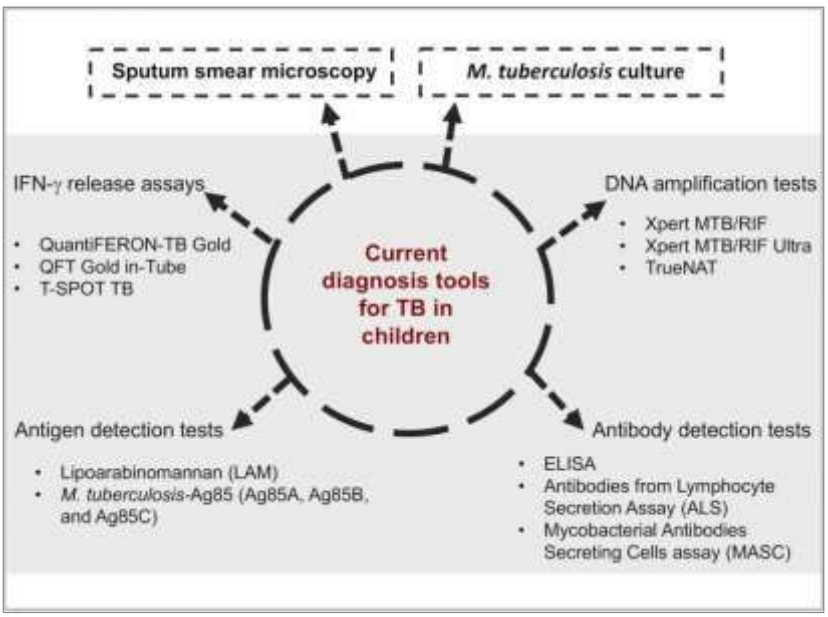

Figure 3: Current tools to diagnose TB in children. The traditionally denominated golden standards microbiological culture and sputum smear microscopy set the diagnosis in adults, but children are challenging to prove positive for either of them. Currently, diagnosis in children should include one or more of the more sophisticated techniques.

i. Newer Drugs for Drug-Resistant TB - The management of drug-resistant TB has changed substantially with the introduction of newer and repurposed drugs, particularly bedaquiline, pretomanid, delamanid and linezolid. These agents have enabled the

development of shorter, predominantly or completely oral treatment regimens and have reduced reliance on injectable drugs. WHO's 2025 recommendations include a 6-month all-oral BDLLfxC regimen - bedaquiline, delamanid, linezolid, levofloxacin and clofazimine - as an option for MDR/RR-TB, including certain patients with fluoroquinolone resistance.

ii. BPaLM and BPaL Regimens - The BPaLM regimen - bedaquiline + pretomanid + linezolid + moxifloxacin - is a 6-month all-oral regimen recommended by WHO for eligible patients with MDR/RR-TB. When fluoroquinolone resistance is documented, moxifloxacin is omitted, producing the BPaL regimen. These regimens represent an important shift toward shorter treatment with fewer drugs and no injectable agents.

iii. Delamanid and Other Emerging Agents - Delamanid, another nitroimidazole, inhibits mycobacterial cell-wall components and has an established role in DR-TB treatment. It is also being incorporated into newer combinations, including the BDLLfxC 6-month regimen. Beyond currently available drugs, the TB pipeline contains investigational compounds such as telacebec (Q203), sutezolid, delpazolid, pretomanid-related combinations, BTZ-043, TBAJ-876 and quabodepistat, reflecting efforts to develop drugs with new mechanisms of action and activity against resistant strains. These investigational agents should be distinguished from medicines that are already recommended for routine clinical use.

iv. Relevance to Children and Women - For children, the major advances are rapid molecular diagnosis, improved detection of rifampicin resistance, and development of age-appropriate, dispersible and child-friendly treatment formulations. Because pediatric TB is frequently paucibacillary, molecular tests may still be negative despite clinically suspected disease; therefore, diagnosis should integrate microbiological, clinical and radiological evidence.

For women, particularly during pregnancy and lactation, newer TB drugs require careful consideration of available safety evidence, potential maternal–fetal effects and drug interactions. Treatment decisions therefore need to incorporate drug susceptibility, pregnancy status, disease severity and individual risk–benefit assessment rather than applying a uniform regimen.

- **NTM as a Clinically Relevant Differential and Diagnostic Consideration in Children and Women**

In children, non-tuberculous mycobacteria (NTM), also referred to as environmental mycobacteria, constitute an important differential diagnosis of tuberculosis (TB). Clinically relevant species

include members of the Mycobacterium avium complex (MAC) such as *M. avium* and *M. intracellulare*, as well as *M. scrofulaceum*, *M. kansasii*, *M. abscessus*, *M. fortuitum*, and *M. chelonae*. In immunocompetent children, NTM commonly presents as cervical lymphadenitis, whereas pulmonary and disseminated infections may occur particularly in children with underlying immune abnormalities. The clinical, radiological and histopathological features may overlap with TB, and detection of acid-fast bacilli alone cannot establish *M. tuberculosis* infection. Consequently, culture followed by species identification or rapid molecular methods is important when NTM infection is suspected.

In women, NTM should be considered as a differential diagnosis in patients presenting with pulmonary, extrapulmonary, or occasionally genitourinary mycobacterial disease. Important organisms include MAC (M. avium, M. intracellulare), *M. kansasii*, *M. abscessus* complex, *M. fortuitum*, *M. chelonae*, and other rapidly growing mycobacteria. Although NTM infection of the female genital tract is uncommon, it may occasionally produce clinical or histopathological findings resembling female genital tuberculosis (FGTB). This distinction can be particularly relevant in women presenting with infertility, chronic pelvic symptoms, granulomatous inflammation, or persistent genital-tract infection without definitive evidence of *M. tuberculosis*. Pulmonary NTM disease may similarly mimic pulmonary TB, especially in women with chronic respiratory symptoms and compatible radiological abnormalities.

From a diagnostic perspective, acid-fast bacilli (AFB) smear positivity does not differentiate *M. tuberculosis* from NTM. Molecular assays capable of identifying the *M. tuberculosis* complex, mycobacterial culture, and species-level identification are therefore important in diagnostically challenging cases. This distinction is clinically significant because NTM species differ considerably in antimicrobial susceptibility and therapeutic requirements, and prolonged empirical anti-TB treatment may be inappropriate when the underlying infection is caused by NTM. Thus, consideration of NTM alongside *M. tuberculosis* and other acid-fast bacilli strengthens the differential diagnostic approach to mycobacterial disease in both pediatric and female populations (Daley *et al.*, 2020).

I. Conclusion

Tuberculosis in children and women represents a biologically and clinically heterogeneous challenge requiring age-, sex-, and context-responsive approaches to diagnosis, treatment, prevention, and long-term care. In India, the National Tuberculosis Elimination Programme (NTEP) provides the principal framework for coordinated TB control through the integrated Detect–Treat–Prevent–Build approach, encompassing early diagnosis, rapid molecular testing,

drug-susceptibility testing, appropriate treatment, TB preventive treatment, contact investigation, nutritional and social support, and community engagement. The programme was established as NTEP in 2020, building on the earlier Revised National Tuberculosis Control Programme, with the objective of accelerating progress towards TB elimination.

India has articulated an ambitious national commitment to end the TB epidemic by 2025, five years ahead of the global Sustainable Development Goal timeline of 2030. This 2025 target should be regarded as the declared national policy target rather than a confirmed date by which elimination has been achieved. Continued transmission, drug-resistant TB, diagnostic gaps, socioeconomic and nutritional vulnerabilities, and inequalities in access to healthcare indicate that sustained and intensified interventions remain necessary beyond the original target year.

For children, particular emphasis is required on recognition of paucibacillary and extrapulmonary disease, early investigation of household contacts, TB preventive treatment, age-appropriate diagnostics and drug dosing, and prevention of severe forms such as disseminated TB and TB meningitis. In women, integration of TB services with maternal, reproductive and primary healthcare is essential, particularly for pregnancy-associated TB, postpartum disease, female genital TB, infertility, drug-resistant TB, and treatment-related maternal and infant considerations. Differentiation of *M. tuberculosis* from non-tuberculous mycobacteria should also be incorporated into diagnostic pathways where clinically indicated.

Future progress towards TB elimination in India will depend on sustained strengthening of NTEP, expansion of rapid and sensitive diagnostics, improved detection of drug resistance, shorter and effective treatment regimens, preventive interventions, nutritional and social support, community participation, and research addressing the biological differences between children and women. Although 2025 represented India's original national elimination target, TB elimination remains an ongoing public-health objective rather than an endpoint achieved solely by a calendar year. Continued implementation of NTEP and alignment with the broader WHO End TB goal for 2030 will therefore remain important for reducing TB incidence, mortality, transmission, and catastrophic socioeconomic consequences in India.

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