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Review

Emerging evidence to reduce the burden of tuberculosis in children and young people

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ABSTRACT

Tuberculosis (TB) remains a major global health challenge. Children, adolescents, and young mothers are high-risk populations for TB with unique challenges and needs. Children are often misdiagnosed or diagnosed too late, resulting in long-term sequelae or mortality, while adolescents, despite having more recognizable adult-type TB and being an important source of community transmission, can be difficult to engage in care as they often fall between pediatric and adult models of care. TB during pregnancy poses significant risks to the mother-infant pair, yet antenatal screening to ensure timely treatment initiation is often inadequate. Recent research advancements to address these challenges include more accessible TB management aids, shorter effective drug regimens, child-friendly drug formulations, strategies for active case finding to expand treatment coverage including of asymptomatic disease, and more options for preventive therapy. These advances have informed global policy and guidelines; however, major gaps in translation from policy to practice remain. This narrative review discusses the progress and identifies potential solutions with insights from the Asia-Pacific region to ongoing challenges in TB detection, treatment, and prevention in children and young people, with a view to TB elimination.

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Introduction

Globally, an estimated two million children (0-9 years) and adolescents (10-19 years) develop tuberculosis (TB) each year [1]. TB is a major cause of death in children and adolescents, especially young children (0-4 years). Adolescents with TB also represent a critical source of *Mycobacterium tuberculosis* (*M.tb*) transmission, as they commonly have infectious TB and large social networks [2]. Pregnancy and the post-partum period are associated with an increased risk of TB, with important consequences for the fetus or newborn, including intrauterine growth restriction, preterm delivery, stillbirth, and congenital TB [3]. Importantly, TB can cause post-TB lung dysfunction or neurological disability in children and young people; these sequelae are often under-recognized and suboptimally managed in low-resource settings [4,5].

The quantity and quality of evidence to improve TB care in children and adolescents has increased markedly in recent decades (S1, S2). This state-of-the-art review highlights recent advances in evidence-based solutions to address current challenges to improve TB care and prevention in children and young people.

Current global gaps through an Asia-Pacific lens

Wide gaps remain in case detection, treatment coverage, and prevention of TB in children and young people, and these gaps vary between countries [1]. Detection gaps are widest in young children (<5 years) due to the overlap between the clinical presentation of TB and other common childhood illnesses; the reliance on clinical diagnosis due to the paucibacillary nature of childhood TB; and the challenges of obtaining respiratory samples for diagnosis. The diagnostic gap is especially wide for multidrug-resistant (MDR)-TB in children. During adolescence into young adulthood, TB incidence rises sharply with increasing age (1.2). A major hurdle for determining the burden of TB in young adolescents (10-14 years) and older adolescents (15-19 years) has been that notifications have traditionally been reported in age bands of 5-14 years and 15-24 years [2]. The introduction of electronic reporting systems allows for greater disaggregation such as into 5-year bands, but implementation remains inconsistent. The burden of pregnancy-related TB is even more uncertain. In addition to detection challenges, TB programs do not currently request information on pregnancy status when TB cases are notified [3].

Most World Health Organization (WHO)-listed high-burden countries for TB and MDR-TB are in the WHO South-East Asia or Western Pacific regions, referred to collectively as the Asia-Pacific region, accounting for over 60% of people who developed TB in 2023 [1]. The Asia-Pacific region includes diverse epidemiological conditions, local practices, and cultures [6]. This review includes contributions from authors to represent the perspectives of researchers and implementers of TB in young people in a range of countries within the Asia-Pacific region to reflect the current challenges and potential of recent advances to address the challenges.

TB caseload in children varies widely between TB-endemic countries in the Asia-Pacific region; TB notifications in children and young adolescents (<15 years) represent <2% of all TB notifications in Vietnam compared to 25% in Papua New Guinea [1]. The variation across countries is unlikely to be explained by diagnostic limitations alone. Factors that influence TB incidence and caseload in children are listed in Box 1. Seven of the top 10 countries with the largest detection gaps for MDR-TB are in the Asia-Pacific region [1]. The expanding implementation of molecular WHO-approved rapid diagnostic (mWRD) tests is increasing microbiological detection of MDR-TB in the region, but most children with MDR-TB have paucibacillary disease and require a clinical diagnosis. TB services for children are often concentrated at centralized, urban-based facilities, and the coverage of TB preventive treatment (TPT) for recent contacts is very low in most settings [1]. Major gaps remain in the reporting of case notifications or of contact investigation and management [7]. These data are critical for monitoring and evaluation, allocation of resources, procurement needs for diagnostics and drugs and advocacy.

Box 1. Factors influencing tuberculosis incidence and caseload in children.

- Epidemiological – Population demographics
  - Age- and sex-related prevalence of infectious tuberculosis cases
  - Prevalence of risk factors in children (malnutrition; HIV)
- Diagnostic challenges – Clinical overlap with other common illnesses
  - Paucibacillary disease
  - Limited access to diagnostic tools
  - Capacity of health care providers at all levels
- Notification and reporting practices
- Bacille Calmette Guerin coverage
- Screening practices including coverage of contact investigation
- Access to and quality of tuberculosis services for care and prevention
- Detection and treatment coverage of all infectious cases in community

Global policy recommendations have been recently updated based on high-quality evidence, complemented by practice guidelines to support implementation [S1-S3]. Priority activities for national TB programs and child TB working groups representing multiple regions have been identified for implementation and scale-up using existing tools and approaches [6, S4]. Evidence to inform policy updates has often come from outside the Asia-Pacific region and, while highly relevant across many settings, research of approaches to close the gaps in the region is critical. Table 1 lists challenges and considerations to implement programmatic strategies and activities embedded within a “detect-treat-prevent” framework [8].

Opportunities to close the TB detection gap

Improving diagnostic yield and bacteriological confirmation

Bacteriological confirmation should be sought whenever possible in all people with presumptive pulmonary or extrapulmonary TB, including children [9]. Xpert Ultra (Cepheid, Sunnyvale, USA) has higher sensitivity than first-generation tests like Xpert MTB/RIF and TrueNat in children; Xpert Ultra is, therefore, recommended by WHO as a frontline diagnostic test in children and adolescents with presumptive TB [S1]. Access to GeneXpert® platforms at lower-level facilities is increasing but remains variable, with availability lowest in the WHO South-East Asia region (~40% of primary care facilities) [1]. mWRDs can be used on a variety of samples, such as stool, nasopharyngeal aspirates, lymph node aspirates, cerebrospinal fluid, sputum, or gastric aspirate [9, S3]. A recent Cochrane review reported that in children with pulmonary TB, the sensitivity compared to the culture of Xpert Ultra using stool (56%) or nasopharyngeal aspirate (44%) was lower than that for sputum or gastric aspirate (70-75%), while specificity for all sampling methods was similar (around 97%) [10]. Two parallel or sequential samples from the same or alternative sites provide a higher yield for bacteriological confirmation than one [11].

Table 1
Programmatic challenges and strategies to overcome these barriers.

	Programmatic challenges	Strategies and considerations[a]
Detect and treat	• Policy of centralization of services for child TB • Quality of screening for presumptive TB, diagnostic and treatment decisions • Access to molecular rapid diagnostics and CXR at all facility levels • Treatment decision approaches are required for a range of settings with wide variability in diagnostic capacity • Detection and treatment coverage of children with MDR-TB is low • Distinguishing non-severe from severe disease to determine appropriate regimen and treatment duration • Procurement and distribution of child-friendly formulations of first- and second-line drugs • Nutritional support and integration of care for children and adolescents living with HIV • Routine screening and early detection of TB in high-risk immunocompromised patients including those with diseases requiring immunosuppressive therapy • Contact investigation for TB case detection and treatment has low coverage using a passive, facility-based model • Adolescents usually attend services for TB care that are focused on either young children or adults • Screening for TB in antenatal services is low and symptom screen alone is inadequate • Not all children and young people diagnosed with TB are treated and notified	**Human resources for TB services** • Increase employment of H CWs to match upscaled services, or task-shift staff **Training and support for H CWs** • Provide innovative and widely accessible training to improve clinical decision-making skills of H CWs at all levels of care, coupled with onsite mentorship **Access to new diagnostic modalities and treatments** • Provide improved access to rapid diagnostic tests and CXR at all levels, with appropriate training and quality control • Increase availability of diagnostic tools and tools or guides that strengthen clinical diagnosis of TB, including MDR-TB • Provide training and tools for CXR interpretation in children for both diagnosis and treatment decisions; evaluate CXR AI platforms recently developed for use in children for diagnosis and intrathoracic disease severity for treatment decision • Introduce and evaluate antenatal TB screening including the use of CXR AI and sputum-based molecular diagnostics in addition to symptom screen **Patient-friendly and family-centered care** • Co-design and evaluate adolescent-friendly care integrated within child and adult TB services • Family-friendly clinics where children and adults affected by TB can be seen by the same provider thereby minimizing the burden of visits **Collaboration outside TB program** • Engage and support community and primary health care providers to implement integrated screening of TB contacts of all ages • Introduce or strengthen integrated TB screening and care within other services for high-risk groups—nutrition programs, HIV care, antenatal/perinatal care—and the private sector **Collect and report data to monitor programs** • Support policy development, management guidelines, training, data for decision-making and knowledge translation in both central and peripheral services with continuous monitoring • Strengthen linkage between inpatient and outpatient care at all levels to ensure retention in care and successful treatment outcomes with mandatory reporting on age-disaggregated data in all children and young people diagnosed with TB

(*continued on next page*)

Table 1 (*continued*)

	Programmatic challenges	Strategies and considerations[a]
Prevent	• The coverage of contact investigation and TPT is low and usually reliant on a passive, facility-based model of care • When provided, TPT is usually limited to young child contacts or people living with HIV • The provision of services for prevention for high-risk groups such as household contacts require additional workload for already overburdened health care providers • Contact investigation and TPT are not well integrated into active case-finding activities that focus on detecting TB in adults • Determining eligibility for TPT in adolescents and young adults requires investigations to determine infection and exclude asymptomatic disease • The TPT regimen options have expanded and vary in suitability across ages and by individual preferences • There is a lack of knowledge and common misconceptions including in health care workers about the potential benefits and safety risks of TPT • There is a lack of awareness and education about TB in the community, including caregivers and adolescents, which results in stigma, and contributes to low uptake of TPT • Reporting is not routinely done to monitor and evaluate core programmatic indicators of contact investigation coverage, TPT initiation, and completion • The bacille Calmette Guerin vaccine protection is limited to young children • Infection-prevention-control measures for TB are not always given due attention for children and young people attending health facilities	**Human resources for TB services** • Task-shift to share the additional workload by involving community health care workers and nurses at primary care facilities in integrated screening and care for TB contacts **Training and support for H CWs** • Strengthen community engagement and improve understanding of community members and health care workers about TB infection and the potential benefit of TPT • Develop information, education, and counseling material on TB infection and TPT in the local language Access to new diagnostic modalities and treatments • Improve access to mobile CXR to detect/exclude asymptomatic TB to improve case detection in older child and adolescent contacts and determine eligibility for TPT • Develop and disseminate clear guidelines and dosage charts for TPT options that depend on age, suitability, and availability • Procure and distribute single-drug and fixed-dose formulations for TPT **Expansion of TPT** • Expand TPT eligibility in recent contacts to include HIV-uninfected children and young people of 5 years and older • Improve screening for infection and TPT for at-risk groups outside of the household context: school outbreaks, antenatal care, children, and young people with diseases that require immunosuppressive therapy **Patient-friendly and family-centered care** • Decentralize contact investigation and management with adoption of an active, community-based model of care • Introduce infection-prevention-control measures where TB care and care for children and young people are provided at the same facility **Collaboration outside the TB program** • Consider vaccination in older children or young adolescents as a future strategy once there is evidence of protection and safety for new vaccines **Collect and report data to monitor programs** • Introduce program registers for outcomes of contact investigation and TPT at all levels of care for quarterly reporting to inform cascade of care analysis

[a] Adapted from Zawedde-Muyanja *S,* et al. [8].

ACF, active case finding; CXR, chest radiograph; H CW, health care worker; MDR, multidrug resistance; NTP, National TB Program; TB, tuberculosis; TPT, TB preventive therapy.

As sputum induction and gastric lavage are less feasible at primary care levels, stool, or upper respiratory tract (e.g., nasopharyngeal aspirates) samples are increasingly used. Although the yield of *Mycobacterium tuberculosis* using these samples is lower compared to sputum, the feasibility of their use by health care workers with minimal training and suitability for outpatients means that their use can improve population coverage and is also likely to be cost-effective, as they have the potential to detect more bacteriologically confirmed cases [12,13]. Buccal or tongue swab samples can also be used to detect TB although have variable performance; further research is required to optimize and standardize sample collection [14]. Urine lipoarabinomannan (LAM) testing is another available point-of-care test recommended for use in groups at high risk for mortality, such as those with severe immunosuppression [9, S3]. Urinary LAM has low sensitivity in most children with TB and does not detect resistance.

Evaluation is underway of novel molecular tests, some of which identify a wide spectrum of resistance-conferring mutations [15]. Research is also ongoing to identify sensitive and specific biomarkers to overcome the diagnostic challenge of paucibacillary disease; ideally, these biomarkers could distinguish between disease and infection and be measured at the point of care, with results available at the same visit [16]. A three-gene signature host-response assay performed at the point of care on the GeneXpert platform from a fingerprick sample had a sensitivity of 50% and specificity of 90% for culture-confirmed TB in children, and may be useful for monitoring treatment response [17]. A study is underway in Indonesia to evaluate a range of novel diagnostics and sampling approaches at urban primary care facilities for accessibility, cost, and treatment coverage among children and adults [S5].

Strengthening clinical diagnosis

As it is unlikely that any single test available in the near future will diagnose all TB cases, strengthening clinical diagnosis is a priority, especially at primary and secondary level facilities where most children and adolescents with TB first present. Health care workers at these facilities often lack the knowledge and confidence to diagnose TB. The WHO now recommends decentralized services for children and adolescents with presumptive TB [S1] with evidence from different settings of increased case detection and treatment coverage; ensuring the quality of care is an ongoing challenge [9].

Structured treatment decision approaches (TDAs) to support clinical diagnosis have been developed in many settings, but all approaches have limitations, with a tendency to prioritize sensitivity over specificity, thereby accepting some overdiagnosis as inevitable to improve treatment coverage and reduce TB-related deaths. It is important to minimize overdiagnosis and unnecessary treatment. A sensitive and specific point-of-care biomarker has the potential to be added to a TDA [9,17]. TDAs should also address practical management issues such as evaluation of illness severity, comorbidities, and urgency of treatment; indications for referral; and the use of follow-up visits to help differentiate between TB and other diseases. Field guides for management including DR-TB in children, which include management decisions based on collective expert experience, have been recently updated [S6, S7].

The WHO operational handbook includes a suggested TDA which introduces two scoring systems, one if chest X-ray (CXR) is available and the other if CXR is unavailable [S3]. The scoring systems were developed to support clinical diagnosis using data from >4000 children to determine a cut-off deliberately selected to prioritize sensitivity over specificity [18]. A more specific TDA has recently been developed and validated for children with severe acute malnutrition [19]. The WHO's suggested TDA is now being widely evaluated for feasibility and effectiveness, but evaluations are limited by the lack of a "gold" reference standard. Local adaptations are required given the diversity of health system resources and skill sets, and clinical decision-making by the health care provider who is evaluating the patient remains important. Though global learnings remain relevant, many high TB-burden countries have hierarchical health care structures that are poorly suited to frequent, iterative changes.

CXR is important for diagnosing intrathoracic TB, determining the severity of the disease, considering alternative diagnoses, and confirming eligibility for TPT. If CXR is accessible at the primary care level, correct interpretation is crucial, including determining whether CXR is of sufficient quality for interpretation to diagnose TB and determine disease severity. The implementation of the shortened 4-month regimen for non-severe TB depends on correct CXR interpretation. The Union has developed tools, available in multiple languages, to strengthen these skills [S8-S10]. Mobile CXR with artificial intelligence (AI) software is increasingly used for community screening and case-finding in adults and adolescents. Though yet to be validated in children, these tools have the potential for standardized CXR interpretation with accuracy approximating human readers [20].

Strengthening diagnosis in high-risk populations

Prompt diagnosis is particularly critical in those at risk for severe disease associated with poor long-term outcomes or mortality. Early and effective treatment of TB meningitis is associated with a lower risk of mortality or severe disability. In children with presumptive TB meningitis or disseminated TB, performing a lumbar puncture, and promptly initiating treatment without waiting for diagnostic confirmation is critical for improving outcomes [8]. However, children often have numerous health care visits within complex care pathways before a lumbar puncture is considered, contributing to diagnostic delays and poor outcomes [21]. Host biomarker signatures in blood to diagnose and treat TB meningitis at peripheral levels of care or to expedite referral to tertiary level care show promise but require validation [22]. Non-invasive sampling techniques for Xpert Ultra testing and digital CXR are feasible and acceptable at decentralized levels of care for prompt diagnosis and treatment initiation in high-risk children, such as those with severe pneumonia or severe malnutrition [19,23].

Pregnancy also increases the risk of maternal TB, which presents during pregnancy or postpartum and accounts for 6-15% of all maternal deaths [3,24]. It is associated with poor neonatal outcomes, including an increased risk of preterm birth, low birth weight, and fetal death. Though recommended in areas with high TB-incidence populations, antenatal TB screening is uncommonly practiced. The current WHO symptom screen for pregnant women does not accurately detect TB disease in this population, and the best method for screening during pregnancy is still uncertain [3,25].

Strengthening active case-finding in children and adolescents

There is an increasing number of community-wide active case-finding (ACF) initiatives ongoing in the Asia-Pacific region to find the missing cases, improve treatment coverage, and reduce community transmission [26–29]. These activities mostly incorporate mobile CXR screening with AI irrespective of reported symptoms to identify presumptive TB cases for further diagnostic evaluation. A reduction in the prevalence of infectious TB is associated with a reduction in *M.tb* infection prevalence in young children recently born into those communities, as shown in Vietnam and Pakistan [26,27]. Including children in community-wide screening activities would have limited impact on the primary intended outcome to

sharply reduce transmission; however, increasing the participation of adolescents is important.

ACF activities to detect TB in children are usually targeted at high-risk groups, such as recent TB contacts or immunocompromised children. A major role of contact investigation is to detect and treat co-prevalent active TB cases of all ages. The yield for young child contacts is consistently high; the yield for older children and adolescents is lower but still moderate [30,31]. An important challenge is poor coverage and relying on a passive, facility-based model (i.e., contacts must present to facilities for evaluation). A decentralized model at the household level is now recommended as it improves detection and uptake of treatment among contacts with TB disease or infection [32, S2]. In addition to children and adolescents living with HIV, a less recognized high-risk group for TB is children and young people who require immunosuppressive therapy for conditions such as nephrotic syndrome, inflammatory bowel disease, asthma, rheumatological conditions, or malignancy. In Indonesia, TB incidence is over five times higher in people with systemic lupus erythematosus than in the general population [33].

Improving the diagnosis of infection

Evidence of infection with *M.tb* provides support for clinical diagnosis of TB disease and identifies populations most likely to benefit from TPT. Current tests rely on host immunological response. Diagnostic limitations include lower sensitivity in high-risk populations with compromised host response, including children who are young, malnourished, and/or have severe disease; low specificity of the tuberculin skin test (TST), specifically cross-reactivity with bacille Calmette-Guerin (BCG) and non-tuberculous mycobacteria; and inability to distinguish between infection and disease [S2]. Novel tests include TB skin tests of greater specificity than TST and blood-based immune-gamma response assays that are more easily implemented (i.e., do not require as sophisticated laboratory capacity with a shorter time to result than the previous versions)[S2,34]. There are ongoing evaluation studies in Vietnam and other settings of new diagnostics for infection in adult populations [S11]. However, major challenges remain for implementation and access. No test result can be provided as point-of-care, they are relatively expensive and thus rarely available outside funded research projects, tertiary facilities, or the private sector.

Opportunities for improved treatment

Improving detection and diagnosis is useful only if followed by prompt and effective treatment. Overall, children have better treatment outcomes for drug-susceptible and -resistant TB than adults. Children and adolescents experience fewer serious adverse events, though adherence to treatment completion is a common challenge, especially in adolescents [2]. Advances over the last decade have changed global policy and national program guidelines [S1-S3]. These include: the wide availability of dispersible, fixed-dose combinations to treat drug-susceptible TB in young children; the development of child-friendly second-line drugs; a 4-month regimen for non-severe forms of drug-susceptible TB; recommended use of bedaquiline and delamanid allowing for shorter, all-oral regimens to treat MDR-TB in all ages; and an alternative 6-month regimen to treat TB meningitis (Figure 1).

For programs and individual patients, it is ideal to have short, effective, and safe drug regimens irrespective of severity or age. The SMILE-TB clinical trial (NCT06253715) has recently commenced enrolment in multiple countries including India and Indonesia to evaluate a 2-month regimen for children with drug-susceptible TB that replaces rifampicin and ethambutol with rifapentine and moxifloxacin [S12]. Rifapentine has recently been approved in children of all ages and an appropriately dosed dispersible formulation has been developed; it is currently only recommended in children for TPT regimens [S2].

In TB meningitis, the host inflammatory response which contributes to residual disability, is emerging as an important treatment target [35]. Optimal treatment strategies for TB meningitis could focus on both improved CNS penetration of drugs and target inflammatory pathways which lead to post-TB sequelae with adjunctive host-directed therapy [36]. However, most TBM treatment trials exclude children and even adolescents. To date, there has been just one trial in children with TB meningitis which showed better neurocognitive outcomes in those who received high-dose rifampicin [37]. A multicenter clinical trial of a novel 6-month intensified regimen of four drugs in African and Asian children and adolescents—high-dose rifampicin, high-dose isoniazid, and levofloxacin—compared to the standard 12-month regimen with/without high-dose aspirin has recently completed enrolment [S13]. Clinical trials evaluating meaningful long-term outcomes in children and adolescents are required.

Limited representation of children in clinical trials that require bacteriological endpoints or the use of new drugs means that new evidence does not always translate to policy or eligibility in children. This is illustrated by the 6-month BPaL(M) regimen which is now recommended in adolescents (>14 years) and adults with DR-TB but not applicable to children as pretomanid is not yet licensed for this age group [9]. Sometimes, results have been extrapolated from adults to children, such as for the 6-month BEAT-TB regimen of bedaquiline, delamanid, and linezolid in combination with either levofloxacin, clofazimine or both. This regimen is now recommended for people of all ages with DR-TB [S14]. This approach may be reasonable as all drugs in this regimen can be used in children, and outcomes and tolerability are assumed to be at least as good as in adults. However, this approach ignores specific clinical and developmental outcomes. For example, children with MDR-TB tend to have less severe disease and better treatment outcomes compared to adults, and a shorter exposure to linezolid could have possibly similar outcomes but much less drug-related toxicity [38].

Opportunities for improved care

The effective management of comorbidities such as malnutrition, anemia, diabetes, or immunocompromising conditions is critical for optimizing TB treatment outcomes [9, S3]. Malnutrition is a very common comorbidity in the Asia-Pacific region [1] and is associated with poorer treatment outcomes in children and adults, especially those with DR-TB. Therefore, nutritional support is crucial as is screening for and management of HIV [39]. Social protection and minimizing the financial and psychosocial burden of TB are essential for TB drug adherence and cure. Along with treatment support, mitigating stigma and providing services that are responsive to the needs of young people are important for optimal engagement in TB care and successful treatment outcomes [40]. Decentralized and integrated models of care increase access to care and treatment coverage while reducing costs to families and health systems. However, effective implementation to achieve successful treatment outcomes should always be person-centered with consideration of individual needs and pragmatic local solutions. Furthermore, a multisectoral approach will allow broad interventions to target social and structural determinants of TB thereby improving overall care for children and young people.

Opportunities to improve care for adolescents and young adults

TB case notifications and estimated incidence rise sharply in older adolescents and young adults (AYAs; 15-24 years) in most TB-endemic countries. TB is a leading cause of death in AYAs in

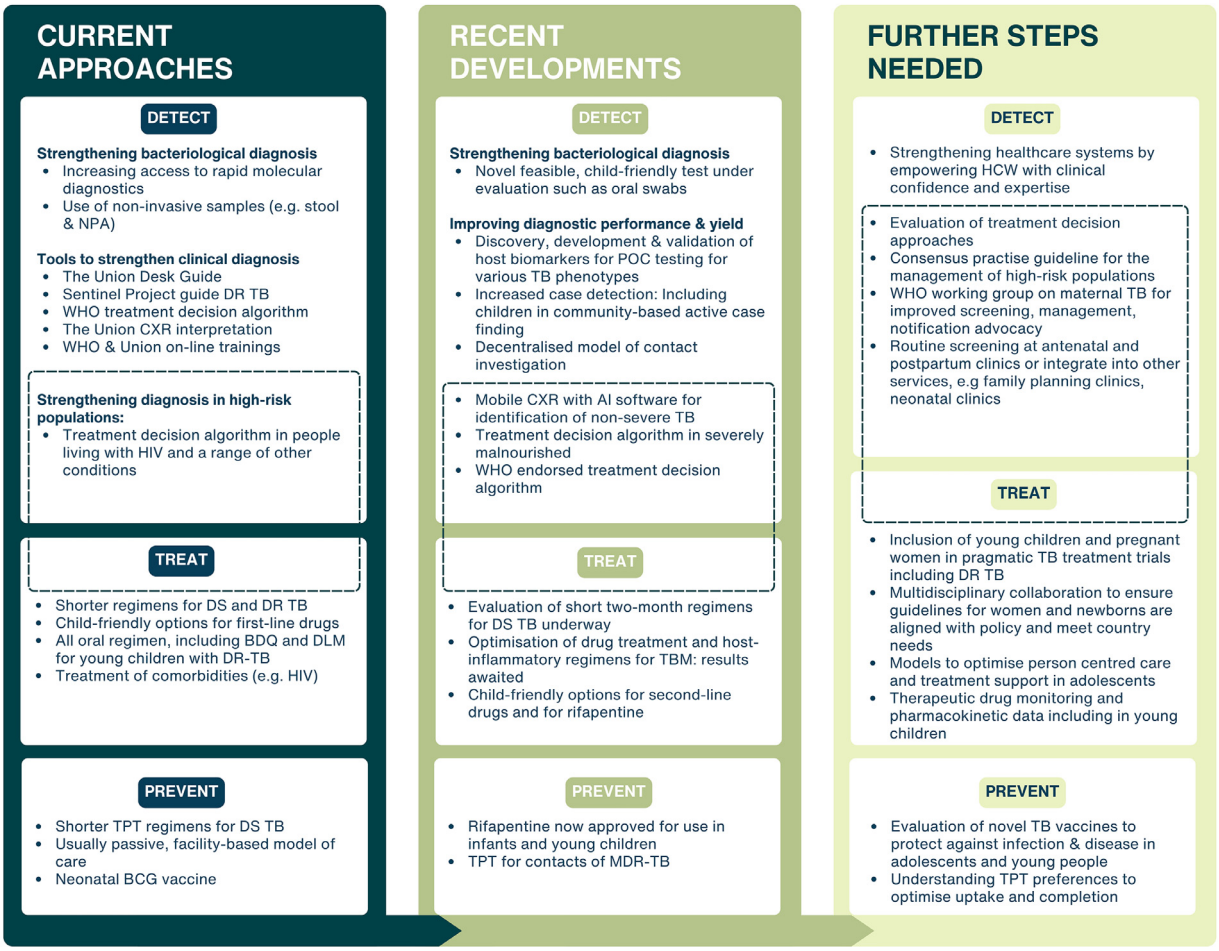

Figure 1. Strengthening the cascade of TB care: innovations in detect, treat, and prevent. Tools to detect and treat (e.g., treatment decision algorithms) often overlap and are represented as both by boxes with broken lines. There are several recent developments in TB detection, treatment, and prevention. Gaps in TB care and control remain, notably a paucity of evidence-based recommendations and practice guidelines for maternal and perinatal TB and improved TB care for adolescents. Decentralized models of care are crucial to TB detection and treatment coverage, while local implementation research is critical to evaluating the impact of these detect-treat-prevent interventions, on TB caseloads and treatment outcomes, in children and young people.
AI, artificial intelligence; BCG, Bacillus Calmette-Guerin; BDQ, bedaquiline; DLM, delamanid; DR, drug resistant; DS, drug susceptible; CXR, chest radiograph; H CW, health care worker; MDR, multidrug-resistant; NPA, nasopharyngeal aspirate; POC, point-of-care; TB, tuberculosis; TPT, TB preventive therapy; TBM, tuberculous meningitis; WHO, World Health Organization.

many Asia-Pacific countries [S15]. AYAs play a key role in community transmission and outbreaks in student boarding residences are a particular challenge in some countries, such as Mongolia, China, and Indonesia [41]. A needs assessment survey by WHO of 1143 adolescents from 104 countries found that they experience many barriers to accessing health care and often lack the knowledge and experience to recognize the need to seek health care and to navigate often-complex health systems [S16]. With respect to TB, this challenge manifests as poorer treatment adherence—missed doses and/or loss to follow-up—relative to other age groups. Loss from treatment is associated with HIV co-infection and previous TB treatment. Recent data from South America showed that pregnant AYAs are more likely to experience loss from TB treatment than their non-pregnant peers and that caregiver support protects against suboptimal adherence [42,43].

TB disease and treatment have the potential to disrupt AYA's cognitive and socioemotional development [44]. Box 2 lists some of the unique aspects to consider for the provision of TB care for AYAs. Despite the difficulties faced by AYAs, their specific needs have only recently been addressed in policy and advocacy [S1-S3]. Two resources can be used to make TB services more adolescent-friendly [40, S16]. Both emphasize person-centered care and a balance between AYAs' growing autonomy and the benefits of supportive caregivers [9]. Other key recommendations include reporting disaggregated surveillance data stratified by 5-year age bands; strengthening sources of community support, including providing resources to help family members better support AYAs and recruiting AYA TB survivors to support those currently on treatment; providing health literacy education; screening and addressing psychosocial needs; ensuring that confidentiality is maintained between adolescents and health providers; and minimizing interruptions to education and employment. The implementation of such initiatives also has the potential to reduce TB-related stigma which is commonly experienced by AYAs with TB. Engaging adolescents in the planning, monitoring, and evaluation of health care provision is an additional standard for quality health services for adolescents [40, S16].

Box 2. Psychosocial aspects unique to adolescents and young adults with tuberculosis.

- Educational setbacks due to exclusion from classes
- Learning difficulties due to TB disease (e.g., fatigue) or tuberculosis treatment (e.g., hearing impairment)

- Mental health deterioration due to treatment effects, isolation, and stigma
- Schedule conflict between classes and medical appointments
- Social isolation from friends and other peers
- Increased risk of depression due to physical effects of tuberculosis and its treatment
- Isolation with anticipated and experienced stigma, threat to schooling and work
- Substance abuse and related side effects
- Impaired effectiveness of contraception by rifamycin

Opportunities to close the TB prevention gap

BCG vaccine protects against severe forms of TB in young children. Modeling suggests that the most effective contribution to TB control, and therefore child TB caseload in high-burden settings, would be a vaccine that prevents more infectious forms such as pulmonary TB in AYAs [45]. A phase III randomized controlled trial including study sites in Indonesia, is underway to evaluate the efficacy of the M72/AS01E TB vaccine which showed promise in phase IIb evaluation [46]. With respect to nutritional interventions to prevent TB, the RATIONS trial has provided compelling clinical trial data to support long-standing knowledge that improving nutrition protects against TB disease [47]. In vitamin D-deficient Mongolian schoolchildren, vitamin D supplementation did not reduce the risk of TB infection or disease compared to placebo [48].

The use of TPT for high-risk groups such as young child contacts has been supported by decades of high-quality evidence. The coverage of TPT in eligible recent contacts is improving globally but remains much lower than TPT for people living with HIV [1]. An important advance in recent years is the recommended use of a range of TPT regimens that are shorter, effective, safe and that can be provided using child-friendly formulations with durations of 1- to 3 months delivered daily or weekly for contacts of drug-susceptible TB [S2]. Evidence from placebo-controlled trials in contacts, including children and young people, without TB disease who were infected following exposure to people with fluoroquinolone-susceptible MDR/RR-TB demonstrated that 6 months of daily levofloxacin reduced the risk of TB disease by around 50%, with few severe adverse effects [49]. These studies informed a WHO recommendation update in 2024 [S3] and align with practices already being introduced in some high-risk populations [28]. Another critical change to recommendations is that HIV-negative child and adolescent contacts of $\geq$5 years who do not have active TB are also routinely eligible for TPT [S2, S3]. The effectiveness of TPT in contacts across age ranges has recently been summarized [50]. The main limitations of current diagnostics to identify those most likely to benefit from TPT have been highlighted above; access is a major challenge for most populations who would benefit. Screening for disease and treatment of infection with TPT should be routine in those with immunocompromised conditions or receiving immunosuppressive therapy, but research evaluating potential benefits to patient outcomes is currently limited. Further research is also required to determine the risks and benefits of TPT during pregnancy [3].

A recent cluster-randomized trial showed that an active household-based approach is superior to a passive, facility-based approach; providing wider coverage of contact investigation and increased TPT initiation and completion rates [32]. Task shifting of contact management to community health workers, supported by staff at the primary care level, can achieve high levels of TPT initiation and completion while increasing detection of active TB. TPT can be initiated in young child contacts (<5 years) because of a negative symptom screen alone [S1, S2]. However, the need for a CXR to detect or exclude asymptomatic TB becomes an important consideration among older contacts such as AYAs.

Summary

TB among children and young people remains a significant burden and global public health challenge. There is increasing high-quality evidence for improved diagnostic approaches suitable for all levels of care, shorter and effective child-friendly treatment, and successful prevention strategies for all age groups including for DR-TB, however, major gaps in TB care persist. Addressing these gaps is crucial to reducing TB deaths in children, and community transmission from young people. Figure 1 highlights recent developments and suggested steps forward for impact. Solutions depend on strengthening of the detect-treat-and-prevent cascade, ideally within decentralized and integrated models of care that are adapted to local settings and responsive to the needs of young people.

Declarations of competing interest

The authors have no competing interests to declare.

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Author contributions

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Supplementary materials

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