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Paediatric tuberculosis – new advances to close persistent gaps

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ABSTRACT

Young children are most vulnerable to develop severe forms of tuberculosis (TB) and are over-represented among TB deaths. Almost all children estimated to have died from TB were never diagnosed or offered TB treatment.

Improved access to TB preventive treatment (TPT) requires major upscaling of household contact investigation with allocation of adequate resources. Symptom-based screening is often discouraged in adults for fear of generating drug resistance, if TB cases are missed. However, the situation in vulnerable young children is different, as they present minimal risk of drug resistance generation. Further, the perceived need for additional diagnostic evaluation presents a major barrier to TPT access and underlies general reluctance to consider pragmatic decentralised models of care.

Widespread roll-out of Xpert MTB/RIF Ultra® represents an opportunity for improved case detection in young children, but attaining full impact will require the use of non-sputum specimens. The new Fujifilm SILVAMP TB LAM® urine assay demonstrated good diagnostic accuracy in HIV-positive and malnourished children, but further validation is required. Given the limited accuracy of all available tests and the excellent tolerance of TB drugs in children, the global community may have to accept some over-treatment if we want to close the persistent case detection gap in young children.

Background

The COVID-19 pandemic has amplified global tuberculosis (TB) control challenges with likely increases in TB incidence and mortality (Anon, 2020a; Zumla et al., 2020). Reduced case finding, increased diagnostic delay and TB treatment interruption all increase community transmission of both drug-susceptible and drug-resistant TB. Since TB disease rates in children reflect community transmission (Marais et al., 2005), there is a grave concern that the TB disease burden in children will increase as a result of the global disruption caused by COVID-19.

Young children (<5 years of age) in particular struggle to access TB care, are most vulnerable to developing severe forms of disease

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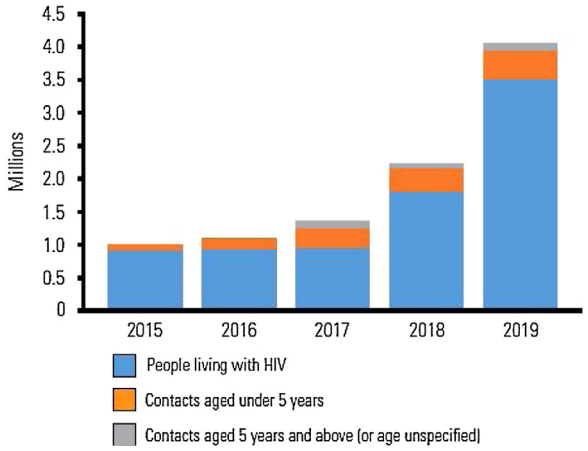

Figure 1. Global increase in tuberculosis preventive therapy (TPT) provision since 2015*.
*from the WHO Global Tuberculosis Report 2020 (Anon, 2020a).

and are over-represented among TB deaths (Perez-Velez and Marais, 2012; Dodd et al., 2017). They should therefore be a key target group for TB preventive treatment (TPT). Although TPT provision nearly doubled from 2018 to 2019 (2.2 and 4.1 million people treated in respective years), most of the increase occurred among people living with human immunodeficiency virus (HIV), reflecting prioritization of TPT targets by major HIV programme donors (Figure 1). The number of household contacts to whom TB programmes provided TPT increased only modestly from 423 607 in 2018 to 538 396 in 2019 (Anon, 2020a), suggesting that TB programmes remain poorly equipped to execute routine household contact management. Even among vulnerable young children, only a third of these estimated 1.3 million eligible child household contacts received TPT. These numbers fall far short of targets formulated at the 'United Nations high level meeting on the fight against TB' in 2018 (Anon, 2021a).

Figure 2 reflects persistent gaps in case detection in relevant age groups.

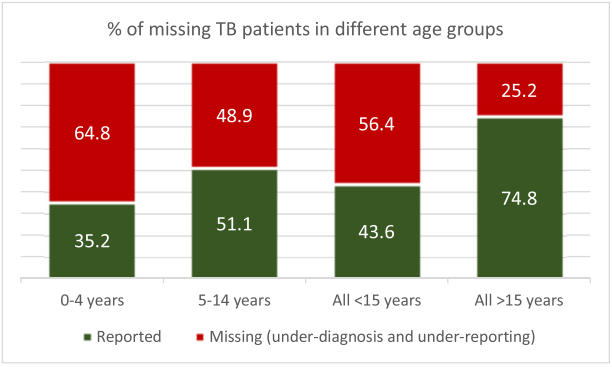

Figure 2. Estimated global TB case detection gap in different age groups, 2019*.
*from data reported to WHO for the 2020 Global Tuberculosis Report.

Closing the TB prevention gap

Improved access to TPT requires major upscaling of household contact investigation, with updating of national strategies and allocation of adequate resources - in line with revised World Health Organization (WHO) recommendations (Reuter et al., 2020; Anon, 2021b). The prioritization of household contact investigation is important for TB prevention, as well as for active TB case-finding (Fox et al., 2019; Dodd et al., 2018). Although the majority of TB transmission occurs in the community (Martinez et al., 2019), household exposure offers an efficient route for intervention, while challenges of TB diagnosis further elevates the importance of TPT delivery in vulnerable young children. Some progress has been made with 121 countries reporting the use of TPT in child contacts under 5 years of age in 2019, including 32 of the 38 high TB and TB/HIV burden countries (Anon, 2020a). At a country level, India reported the highest number of TPT courses (around 100 000) provided to young children in 2019; this number pales in comparison to the 1.9 million pulmonary TB cases notified and the number of child contacts associated with these (Anon, 2020a; Anon, 2021c). Table 1 provides an overview of new advances and persistent challenges in closing the TB prevention gap.

Table 1
New advances and continuing challenges to close persistent gaps in tuberculosis preventive treatment (TPT) provision and tuberculosis case detection in children.

New advances	Continuing challenges
TPT provision	
New WHO guidance	No dedicated funding for household contact management; limited monitoring and evaluation
Shorter and more child-friendly treatment	Absence of a simple and validated screening test for rapid triage
Improved reporting in some settings	Different opinions regarding the risks of symptom-based screening in adults and children resulting in inconsistent communication; resistance to task shifting required for decentralized TPT initiation
	Lack of pediatric data and availability of child-friendly formulations of rifampicin and rifapentine
	Management of RR/MDR-TB contacts, especially in the presence of quinolone resistance
TB case detection	
Improved awareness and training	No current test with sufficient diagnostic accuracy (may have to accept some degree of over diagnosis, especially in the youngest and most vulnerable age group)
Increased sensitivity with Xpert MTB/RIF Ultra®	Absence of an accurate reference standard complicates assessment of new diagnostics; wide and mostly pauci-bacillary disease spectrum necessitates evaluation against both microbiologic and clinical reference standards; incorporation bias when using a clinical reference standard may result in overestimation of test accuracy
Stool approved for use as a 'respiratory specimen' thereby, facilitating specimen capture in young children who cannot expectorate	Promising host biomarker profiles identified, but not yet 'field ready' development hampered by lack of an accurate reference standard
Increased diagnostic accuracy from urine with SILVAMP TB LAM®; particular value in HIV-positive and malnourished children	Sub-optimal integration of care between TB programmes, paediatric and MCNH services, including limited private sector involvement
First evidence-based TB treatment decision score for HIV-positive children	

HIV – human immunodeficiency virus; MCNH – maternal, child and neonatal health; MDR – multidrug (rifampicin and isoniazid) resistant; RR – rifampicin resistant; TB – tuberculosis; TPT – TB preventive treatment; WHO World Health Organization.

Recent advances include new WHO guidelines and a detailed implementation handbook released in 2020 (Anon, 2021b; Anon, 2021f). There is a need to differentiate the main focus of contact investigation in vulnerable young children, which is to prevent TB disease and death soon after primary infection through the provision of TPT (Perez-Velez and Marais, 2012; Martinez et al., 2020), from the emphasis in older individuals that includes attempts to decrease transmission and promote epidemic control. Current WHO child TB guidance advises symptom-based screening of high-risk contacts (Anon, 2014), which has been shown to be effective in a prospective study in Indonesia (Triasih et al., 2015a). These symptom-based approaches have been developed with consideration of resource constraints and important differences in the TB disease risk and spectrum between young children and adolescents or adults.

The high disease risk in young children with recent TB exposure provides urgency to give TPT and decreases the number needed to treat to prevent one case of TB (Anon, 2021f; Mandalakas et al., 2020). TPT is also extremely well tolerated in young children and given the pauci-bacillary nature of their disease there is minimal risk of inducing drug resistance, even if disease is missed by symptom-based screening. In fact, there is every expectation that TPT would be curative in young children with minimally or asymptomatic disease; defined as the presence of intra-thoracic lymphadenopathy suggestive of TB on chest radiography (or even microbiological confirmation) in the absence any significant symptoms (Marais et al., 2009).

The situation is different in adolescents and adults where people with minimal symptoms could have multi-bacillary disease (Marks et al., 2019), requiring an Xpert MTB/RIF test and/or chest radiograph to rule out TB disease before TPT initiation. This important distinction is rarely appreciated, and TB programmes struggle to implement differentiated strategies that best serve the needs of children. Xpert MTB/RIF testing is not appropriate in asymptomatic children before starting TPT, since testing is expensive and availability is often limited, respiratory sampling is invasive and the yield is extremely low. Good quality paediatric chest radiography may provide additional case detection value, but it is rarely available in resource-limited settings, its relevance is uncertain in asymptomatic child contacts and interpretation is hampered by poor inter-observer agreement (Triasih et al., 2015b). From a patient perspective, parents often need to travel long distances at their own expense with additional out-of-pocket costs to complete chest radiography. Together these factors mean that chest radiographic screening poses a major and unnecessary barrier to TPT access in resource-limited settings and limits the roll-out of decentralised models of care.

There is a common misperception that there is a need to document TB infection by performing a tuberculin skin test (TST) or interferon gamma release assay (IGRA) prior to initiating TPT. While these tests have value in establishing TB infection in individuals who may benefit from TPT (Mandalakas et al., 2020), their added value in close contacts of an infectious TB case is limited, especially in high incidence settings where rates of past TB infection are high. Their added value is also less clear in vulnerable young contacts in whom careful consideration should be given to sensitivity concerns and the post exposure 'conversion window'. Existing international guidance encourages decentralised TPT provision for close contacts, without the need for TB infection testing (Anon, 2021b; Anon, 2021f; Anon, 2014).

Expanded TPT options now include child-friendly dispersible fixed dose combination tablets of daily rifampicin and isoniazid for 3 months (3RH), 12 weekly doses of rifapentine and isoniazid (3HP) or a daily dose for 1 month (1HP; recently also available as a fixed dose combination tablet), a daily dose of rifampicin for 4 months (4R) and traditional daily isoniazid for 6-9 months (6-9 H) (Anon, 2021c). At present, 3RH using child-friendly combination tablets (available through the Global Drug Facility; GDF) is the preferred regimen for children up to 25 kg; 3HP can be used from age 2 years but lacks a child-friendly option; 1HP is only recommended from 13 years of age and 4R also lacks a child-friendly formulation. In general, the use of isoniazid monotherapy (6-9 H) remains the preferred option in children living with HIV who are on antiretroviral therapy; dispersible 100 mg tablets are available through the GDF. The development of child-friendly dispersible rifapentine tablets for use in TPT and shortened TB treatment regimens is a key priority, as is finding better solutions for children exposed to drug resistant TB in whom traditional TPT is likely to be ineffective (Huynh et al., 2020).

Despite the availability of expanded and more child-friendly regimens, TPT implementation and scale-up will only be achieved if it is perceived as a priority by TB programmes and major donors (as it is for HIV programmes), with clear goals, a practical implementation plan, reliable drug supply and effective monitoring and evaluation systems. There is an urgent need to explore creative task shifting for TPT initiation to facilitate decentralised patient-centred options for service delivery – at least in vulnerable young children in whom the benefit:risk ratio is highest (Zawedde-Muyanja et al., 2018). A large multi-centre implementation study in Benin, Burkina Faso, Cameroon and the Central African Republic (the TITI study) demonstrated the feasibility of this approach with excellent TPT initiation and completion rates, almost no adverse events and no indication of TPT failure (Schwoebel et al., 2020). A formal cluster randomized study in Cameroon and Uganda (the CONTACT Study) is currently assessing the feasibility and cost-effectiveness of community-based household child contact screening and TPT initiation using 3RH.

Closing the TB case detection gap

TB is now recognised as a top-10 killer of children under 5 years of age (Dodd et al., 2017), although estimating the burden of TB disease in children remains challenging given the inconsistent quality of notification data (Anon, 2020a). Almost all children estimated to have died from TB were never diagnosed or offered TB treatment (Dodd et al., 2017), which is a tragedy given that children have excellent TB treatment outcomes - even with drug-resistant disease (Huynh et al., 2020). Widespread roll-out of Xpert MTB/RIF represents a major advance on traditional smear microscopy and has been endorsed by WHO as a front-line diagnostic test for pulmonary and extra-pulmonary specimens (Anon, 2020b). It is important that Xpert MTB/RIF should be made available for testing of children in high TB incidence settings where access was previously restricted to sputum specimens only, effectively excluding children who are unable to expectorate.

Alternative respiratory samples in young children who reflexively swallow their sputum, include induced sputum, gastric aspirates, nasopharyngeal aspirates and stool, while excellent yields have been reported in various non-respiratory samples (Anon, 2020b). The recently released Xpert MTB/RIF Ultra® cartridge was developed for increased sensitivity and should provide added value in children with pauci-bacillary disease, although indications are that sensitivity remains sub-optimal and the high cost of testing multiple specimens to increase the diagnostic yield remains a major barrier (Schaaf and Marais, 2019). Urine lipoarabinomannan (LAM) is recognised as a useful 'rule-in' test to assist TB diagnosis in people living with HIV, but inconsistent diagnostic accuracy has been reported in children (Nicol et al., 2020). The new Fujifilm SILVAMP TB LAM® assay has improved diagnostic accuracy and offers particular value in HIV-positive and malnourished children, in whom the diagnostic dilemma is most pronounced, but the test is not yet commercially

available and has not been evaluated by the WHO (Nicol et al., 2020).

The Unitaid-funded multi-country TB-Speed project (https://www.tb-speed.com/) is testing a variety of diagnostic approaches, including clinical/radiological algorithms and laboratory tests in children hospitalized with severe pneumonia, children with severe acute malnutrition, HIV-positive children, and children identified with presumptive TB in the general population. It is also assessing different sampling strategies with the aim of improving access to molecular testing for children. Good advances have also been made on the biomarker front, although the variable spectrum of disease and difficult end-point definitions pose particular challenges in young children (Togun et al., 2018; Anon, 2021d).

WHO recently released a Rapid Communication with generally favourable assessment of new computer aided detection (CAD) systems for TB population screening and case detection in adults (Anon, 2020c). Although the performance in older children is likely to be similar to those in adults, children <10 years of age experience a very different and variable spectrum of disease (Perez-Velez and Marais, 2012; Pillay et al., 2020) limiting the usefulness of adult evidence. Other chest imaging advances include more robust and more affordable digital X-rays. High quality X-rays remain an important diagnostic tool, supports clinical training and has added value beyond TB to detect other clinically relevant conditions. Digital X-rays also provide options for remote reading. Point-of-care ultrasound has been explored, but intra-thoracic lymph node visualisation remains difficult and highly operator dependant (Pillay et al., 2020). In HIV-positive children, abdominal ultrasound may assist TB diagnosis by detecting enlarged lymph nodes and splenic micro-abscesses (Sartoris et al., 2020). Sophisticated imaging options for use in referral centres include computed tomography (CT), positron emission tomography (PET)-CT and new rapid magnetic resonance imaging (MRI) protocols (Pillay et al., 2020).

Considering the persistent challenges in laboratory-based diagnosis, it remains critically important to strengthen the capacity of front-line health care workers to clinically suspect and diagnose TB in children (Huynh et al., 2020). Pragmatic approaches providing evidence-based treatment decision support provides a way forward (Marcy et al., 2019). As a global community we will have to accept a degree of over-treatment if we want to close the case detection gap in children. The SHINE trial demonstrated that 4-months is non-inferior to 6-months of TB treatment in children with non-severe pulmonary and extra-pulmonary disease. Results will be reviewed by the WHO to refine policy recommendations for the treatment of drug-susceptible TB in children (Anon, 2021e). The fact that regimens used for TPT and treatment of non-severe TB disease in children will likely become very similar in duration (3 months vs. 4 months), challenges the different thresholds applied for treatment access. Given the sub-optimal accuracy of available diagnostic tests, it seems reasonable to accept some over-treatment in vulnerable young children, similar to the way we accept TB exposure as an indication for TPT in a large number of children to prevent TB disease and mortality in a few. In high TB incidence settings, the benefits of such an approach override the potential risks given that these drugs are well tolerated and that the risk of creating drug resistance is minimal in young children.

Conclusion

Closing the persistent gaps in detection, treatment and prevention of childhood TB is essential to meet the End TB goal of zero TB deaths and targets formulated at the 'United Nations high level meeting on the fight against TB'(6). The Roadmap toward Ending TB in Children and Adolescents articulates the urgent need for more basic science and implementation research to find workable solutions for these persistent challenges (Anon, 2018). The 21st century presents novel health and sustainability challenges that require careful re-evaluation of traditional global health approaches, but the need for 'integrated child health' and 'family centered care' included in the principles of Alma Ata (and reconfirmed in the Astana declaration) remain relevant (Detjen et al., 2019).

Including a specific paediatric focus when planning TB services, as well as close collaboration between TB and maternal and child health services, HIV services, private practitioners and the broader paediatric community, are important to provide effective care pathways for children with TB exposure, infection and disease. This will be even more important in the aftermath of the COVID-19 pandemic, as is building on the positive lessons learnt from large scale community mobilization, enhanced infection control and the rapid scientific advances made during this trying time.

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Conflict of interest

None of the authors have any competing interests to declare.

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