

Increasing tuberculosis preventive treatment (TPT) uptake in children

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Global health system disruption caused by COVID-19 reduced tuberculosis (TB) case finding, increased diagnostic delay and interrupted TB treatment, resulting in worsening global TB control with increased transmission of both drug-susceptible and drug-resistant TB (1,2). Since TB disease in children reflects transmission in the community (3), there is an urgent need for improved disease prevention, especially in young and vulnerable children. Children less than 5 years of age and those with immunocompromise are at greatest risk of disease development after TB exposure (3-5), which identifies them as a key target group for post-exposure TB preventive treatment (TPT).

The gap in scaling up TPT for children following TB exposure

The World Health Organisation (WHO) estimates that less than a third of children with documented household TB exposure received TPT in 2020, falling far short of global targets (2). Reasons for poor TPT uptake include broad health system factors such as inadequate investment and the absence of functional monitoring systems, as well as physician perceptions of futility given the ubiquitousness of TB exposure in high incidence settings and data suggesting that most TB transmission to children occurs outside the household (6,7). However, although most TB transmission in high incidence settings occurs in the community, household TB exposure remains an important risk factor for disease development and known exposure offers an easily identifiable and efficient route for intervention (8,9).

TPT delivery is further hampered by perceptions that a positive tuberculin skin test (TST) or interferon-gamma release assay (IGRA) and a normal chest X-ray (CXR) are prerequisites for TPT provision. While TB infection tests are useful to identify children who may benefit from TPT (10), empirical post-exposure TPT is important in vulnerable young or immunocompromised children in whom access to infection testing is limited, the likelihood of a false negative TB infection test is increased and the post-exposure 'conversion window' (TB infection tests take 6-12 weeks to convert to positive after TB infection) requires careful consideration (11). While it is important to improve children's access to high quality CXRs, in practice CXRs are often unavailable in resource-limited settings (11). Restricted CXR availability should not pose an unnecessary barrier to TPT access. In order to increase TPT access in children, recent research findings and new WHO guidelines encourage decentralised TPT provision using symptom-based screening for child TB contacts, without the need for TB infection testing or CXRs - if these are not readily-available and free of charge (12-14).

Another common barrier to TPT provision include physicians' uncertainty about whether caregivers will accept treatment for their children. Anecdotal reports indicate many caregivers are reluctant to give medicine for a prolonged period of time to a child that 'looks healthy', despite their elevated risk of subsequent TB. Given strong evidence for TPT efficacy and safety in children exposed to a patient with drug-susceptible TB, health care workers and caregivers can generally be convinced about its value. Caregiver acceptance has been considered a particular concern in cases where second-line TPT is indicated, following exposure to a patient with multidrug-resistant (MDR) TB, given that efficacy and safety data are more limited.

Caregiver acceptability of TPT

A study by Rouzier and colleagues (15) assessed the willingness of caregivers to give TPT to children living in households of patients with rifampicin-resistant (RR) TB; considered a proxy for MDR-TB. The study was conducted in 8 countries (Botswana, Brazil, Haiti, India, Kenya, Peru, South Africa and Thailand) in preparation for the PHOENix trial (Protecting Households on Exposure to Newly Diagnosed Index MDR-TB Patients). Semi-structured interviews and knowledge, attitudes, and practices questionnaires were completed, with complementary demographic, social, medical and household characteristics data.

Overall, 278 (92.9%) of caregivers were willing to give MDR-TPT to children; willingness was high at all sites [IQR 79-100%]. Higher willingness was strongly associated with TB-related knowledge (odds ratio [OR] 5.1 [95% CI, 2.3,11.3]), belief that one can die of MDR-TB without treatment (OR, 5.2 [95% CI, 1.2-23.4], awareness and concern that the child could get MDR-TB from the index case (OR, 4.5 [95% CI, 1.6-12.4]), confidence in the child's ability to take MDR-TPT for the required duration (OR, 4.5 [95% CI, 1.6-12.6]), being comfortable telling others about the MDR-TB exposure and need to take MDR-TPT (OR, 5.5 [95% CI, 2.1-14.3]) and caregivers' willingness to take TPT themselves (OR, 35.1 [11.0,112.8]). The high willingness of caregivers to give MDR-TPT to children at high risk of MDR-TB infection and disease highlights the value of investing in caregiver TB treatment literacy to support shared decision-making, which engages patients and their families, fosters empowerment and facilitates treatment uptake and adherence. Children who initiated MDR-TPT in previous studies

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reported low rates of adverse effects and high rates of treatment completion, particularly for regimens not containing pyrazinamide (16-18).

Closing the TPT gap

It is important to remember that the main focus of contact investigation and TPT provision in vulnerable young and immunocompromised children is to prevent TB disease and death following primary infection with *Mycobacterium tuberculosis*. Increased uptake of TPT may also have longer-term programmatic TB control benefit, but in children the immediate benefit is during the high-risk period shortly after primary or re-infection (11). Recent WHO child TB guidelines advise symptom-based screening of high-risk contacts in resource-limited settings (14), which has been shown to be feasible and effective in prospective studies from Africa (12,13,19) and Indonesia (20). The need to strengthen person-centred approaches within paediatric TB care is also recognised (21, 22). Critical to improving caregiver willingness to take up effective clinical options, such as TPT, is emphasising both their benefits and their responsive alignment to individual and household's lived contexts (23).

Symptom-based screening approaches in children were developed in recognition of 'real-life' resource constraints in many high TB incidence settings and recognize key differences in the TB risk and disease spectrum between children and adults (11). Since adults, and adolescents who tend to develop adult-type TB, with minimal symptoms can have multi-bacillary disease (24), it is important to use sputum Xpert MTB/RIF and/or CXRs to rule out TB disease before TPT initiation (25). However, excluding co-prevalent TB is less relevant in children, who tend to develop pauci-bacillary disease and in whom the treatments for TB infection and non-severe disease are now very similar. Data from the SHINE trial (26), adopted into new WHO TB guidelines, demonstrated that non-severe TB disease in children can be treated with a 4-month regimen (2 months rifampicin [R], isoniazid [H], pyrazinamide [Z] + 2RH), which very similar to the 3RH regimen preferred for TPT in young children (21). These new data provide further support for symptom-based screening of child contacts in resource-limited settings, although optimal symptom-definition remains important to enhance screening sensitivity and safety (27-29).

Expanded TPT options now include child-friendly dispersible fixed-dose combination tablets of 3RH as daily doses, 12 weekly doses of rifapentine [P] and isoniazid (3HP) or a daily dose for 1 month (1HP; recently also available as a fixed-dose combination tablet), a 4-month daily dose of rifampicin (4R) and the traditional daily 6-9H (Table 1). At present, 3RH using child-friendly combination tablets (available through the Global Drug Facility; GDF) is the preferred option for children (<25kg) who are human immunodeficiency virus (HIV) uninfected. Of the other options 3HP can be used from age 2 years but currently lacks a child-friendly option, 1HP is only recommended from 13 years of age and 4R also lacks a child-friendly formulation in settings without a local compounding pharmacy service. The use of isoniazid monotherapy (6-9H) remains the preferred option in children who are on antiretroviral therapy; dispersible 100mg tablets are available through the GDF.

Child contacts of RR/MDR-TB cases have a substantial risk of developing drug-resistant TB, and may benefit from TPT regimens using second-line antibiotics. Published cohort data and current WHO guidelines (14, 16-18) support the use of therapy for vulnerable children, with antibiotic choice guided by the drug resistance profile of the index case. Three ongoing clinical trials are evaluating the effectiveness and safety of second-line regimens – levofloxacin (VQUIN [30] and TB CHAMP [31]) and delamanid (PHoENIX [32]). Each of these two drugs have child-friendly dispersible formulations. If shown to be effective and well-tolerated, these regimens would substantially increase the acceptability of TPT for RR/MDR-TB contacts among caregivers and clinicians.

Despite the availability of a range of 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). This will require clear goals, a practical implementation plan, reliable drug supply and effective monitoring and evaluation systems. There is also a need to explore ways in which healthcare workers can be encouraged to deliver TPT to children using a more decentralised and adaptive patient-centred approach – at least in vulnerable young children in whom the benefit:risk ratio is highest. Studies in Uganda (12), Benin, Burkina Faso, Cameroon and the Central African Republic (the TITI study; 13), and eSwatini (19) have now demonstrated the feasibility of this approach. A cluster randomized study in Cameroon and Uganda (the CONTACT Study) is due to

report soon and will assess both the feasibility and cost-effectiveness of community-based screening of child household contacts and TPT initiation using 3RH.

Conclusion

Closing the persistent gaps in childhood TB prevention and detection is essential to meet targets formulated at the 'United Nations high level meeting on the fight against TB'. Caregivers willingness to administer RR/MDR-TPT to their children, as reported by Rouzier et al. (15), removes another perceived barrier to TPT uptake. Holistic 'family-centered' models of care, as articulated in the principles of Alma Ata and reconfirmed in the Astana declaration (33), are important to facilitate scale-up of household contact TPT, especially for vulnerable young children.

Conflict of interest

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Table 1. Options for tuberculosis preventive treatment (TPT) in children with household exposure to someone with infectious tuberculosis

TPT options	Comments
<u>DS-TB exposure</u>	
3RH	WHO preferred; water dispersible child-friendly FDC available through the GDF
3HP	Only advised in children >2yrs; currently no child-friendly option available
1HP	Only advised in children >13yrs; currently no child-friendly option available
4R	Require compounding pharmacy to prepare syrup and home refridgerator; can be used as TPT for isoniazid mono-resistant TB
6-9H	WHO preferred in children living with HIV; water dispersible tablet available through the GDF
<u>RR/MDR-TB exposure</u>	
6 levo/moxifloxacin	WHO preferred; ongoing studies
6 delamanid	To be considered if exposed to an index case with levo/moxifloxacin resistant TB; ongoing study

H – isoniazid; P – rifapentine; R – rifampicin
 DS – drug susceptible; FDC – fixed dose combination tablet; GDF – Global Drug Facility; HIV – human immunodeficiency virus; MDR – multidrug resistant; TB – tuberculosis; RR – rifampicin resistant; TPT – TB preventive therapy; WHO World Health Organization