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Ⓐ The Value of Chest Radiography in Tuberculosis Preventive Treatment Screening in Children and Adolescents

Despite existing guidelines and strong commitments to increase tuberculosis preventive treatment (TPT) uptake, the World Health Organization (WHO) estimates that less than one-third of young children (<5 yr) who had household contact with an infectious tuberculosis (TB) case received TPT in 2020 (1). Increased TB transmission resulting from COVID-19 health system disruption accentuates the threat posed to vulnerable young children and people living with HIV, who are key TPT target groups. Recently, WHO extended TPT recommendations to HIV-uninfected older children and adolescents (5–19 yr) who are household TB contacts, and coverage in this group is currently estimated to be less than 5% globally (1, 2).

Barriers to implementation of child TB contact screening and management include the need for pragmatic screening options to deliver community-based TPT (3). Chest radiography has a critical role, both to support a clinical diagnosis of TB and to rule out active disease before initiating TPT; but access to chest radiography is a major hurdle in resource-limited settings (4). It has been demonstrated that symptom-based TB contact screening is safe, and that chest radiography adds little value in asymptomatic young children who receive TPT (5–7). However, despite the available evidence, many clinicians remain uncomfortable providing TPT without a chest radiograph to rule out TB disease, given that chest radiography is routinely performed before TPT commencement in settings without resource constraints.

The value of chest radiography also requires further clarification in older children and adolescents, since the WHO now recommends that older child and adolescent TB contacts with evidence of infection

(or on the basis of known exposure to a bacteriologically confirmed infectious TB case, if a test for infection is unavailable) should receive TPT once TB disease has been excluded (2). The role of chest radiography in this older age group requires better evidence as this is a group that, compared with young child contacts, are more likely to have coprevalent subclinical bacteriologically positive TB detectable by chest radiography (8). Therefore, they are at greater risk of suboptimal outcomes and drug resistance acquisition if not appropriately treated.

Assessing the Value of Chest Radiography for Tuberculosis Contact Screening

In this issue of the *Journal*, Huang and colleagues (pp. 892–900) evaluated the diagnostic and prognostic value of chest radiography in children exposed to TB in Peru and measured the efficacy of isoniazid preventive therapy (IPT) in those with radiographic abnormalities (9). They enrolled 4,468 children with household exposure to bacteriologically confirmed TB who had symptom assessment and chest radiography done. The majority (56%) of contacts were 6 years of age or older, and only 0.1% were HIV positive. Chest radiography was limited to an anteroposterior film, and these were interpreted by experienced readers blinded to the clinical presentation. Those without coprevalent TB (at baseline) were followed for 1 year to assess disease progression (incident TB) risk as well as the protective efficacy of IPT.

Asymptomatic children with abnormal chest radiographs were found to be 25 times more likely to have coprevalent TB and 26 times more likely to be diagnosed with incident TB during follow-up than asymptomatic children with normal chest films (9). The authors concluded that chest radiography is strongly supported as a routine screening tool for the evaluation of child TB contacts, where this is readily available, given that even atypical radiographic findings in asymptomatic children may indicate incipient or subclinical disease.

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Table 1. Overview of the Benefits and Risks Associated with Chest Radiograph and Symptom-based Screening of Child and Adolescent Tuberculosis Contacts

CXR-based Screening	Symptom-based Screening
Benefits	
<ul style="list-style-type: none"> • May detect incipient and sub-clinical disease in children who are minimally or asymptomatic. • Provides greater assurance that disease has not been missed prior to commencing TPT—this is particularly important in older children and adolescents. • Deeply engrained “standard of care” in well-resourced settings with perceived “medicolegal” risk, if omitted. 	<ul style="list-style-type: none"> • Can be applied independent of local resources, also in a decentralized fashion, and facilitates TPT access. • WHO endorsed in resource-limited settings.
Risks	
<ul style="list-style-type: none"> • Could pose a major barrier to TPT provision in resource-limited settings. • May detect and treat irrelevant chest radiograph abnormalities. 	<ul style="list-style-type: none"> • May miss early or subclinical disease—this should be adequately treated by combination TPT regimens at least in young children (<5 yr). • May reduce the impetus to increase child CXR access as a matter of urgency; every effort should still be made to increase children’s access to high-quality chest radiography.

Definition of abbreviations: CXR = chest X-ray; TB = tuberculosis; TPT = TB preventative treatment. Asymptomatic should exclude any current symptoms potentially suggestive of TB, irrespective of duration.

The group that were asymptomatic with an abnormal chest radiograph contributed to 28 (28.9%) of 97 coprevalent or incident TB cases. However, the overall yield in asymptomatic child contacts was very low: 0.79% for coprevalent disease and 0.76% for incident disease (not reported by age group). In the context of a resource-limited setting, such a low yield may not support routine chest radiography for all child contacts, especially not those who are completely asymptomatic. IPT was also found to be highly effective in preventing disease progression, with 82% efficacy against incident TB documented among ‘asymptomatic’ children who had an abnormal chest radiograph at baseline.

Clearly, these important findings require careful consideration for programmatic implementation. This study did have some limitations inherent to TB diagnosis in young children. The symptom definitions used for screening were not optimized for sensitivity (10). The specific radiographic abnormalities suggestive of TB were not reported, including by age group. In the absence of microbiological confirmation, the case definitions used were heavily dependent on chest radiograph interpretation and therefore open to strong incorporation bias. The most common radiographic abnormality reported in asymptomatic young child contacts is perihilar lymph node enlargement (7, 8). However, accurate detection of this pathology by radiography can be challenging, leading to overdiagnosis of TB as well as underdetection, especially if lateral chest radiograph views are not performed. Lastly, 6 months of isoniazid monotherapy may be less effective in programmatic practice than 3 months of rifampicin and isoniazid (3RH), which is associated with higher uptake and completion and is now the preferred WHO TPT regimen for HIV-uninfected child contacts (2). Although the numbers were small, it appears as if the few children who developed incident TB despite receiving IPT were successfully treated with standard first-line therapy, reflecting the low risk of drug resistance acquisition in young children receiving TPT, even if early paucibacillary disease is missed.

Closing the TPT Gap

It is important to remember that the main focus of TPT provision in vulnerable young children is to prevent severe TB disease and death, which provides a strong imperative to improve TPT access. Symptom-based TB screening approaches recognize “real-life” resource constraints in many high-TB incidence settings, as well as key differences in the TB risk and disease spectrum among young children, adolescents, and adults. Arguably, the exclusion of coprevalent TB is less relevant in asymptomatic young children in whom the treatment of infection with 3RH and of nonsevere disease with a new 4-month treatment regimen (2RHZ/2RH) is now very similar (2, 11, 12). The situation in older child and adolescent contacts is different and therefore better age-disaggregated data (differentiating 5–9, 10–14, and 15–19 yr age groups) on TB screening and management approaches, including the utility of chest radiography, are required. Table 1 provides an overview of the benefits and risks associated with chest radiograph and symptom-based screening of child and adolescent TB contacts.

Closing persistent gaps in child TB prevention and detection is essential to meet targets formulated at the United Nations high-level meeting on the fight against TB. (13) In the end, TPT implementation and scale-up will only be achieved if it is perceived as a priority by TB programmes and major donors, as demonstrated by the high TPT coverage in HIV programmes. This will require practical implementation plans, reliable drug supply and effective monitoring and evaluation systems. High TPT uptake and completion rates have been reported in young child TB contacts using decentralized, community-based approaches that limit the use of chest radiography to symptomatic contacts (6, 7, 14, 15). These prospective implementation studies have demonstrated effectiveness and safety with high retention to follow-up following TPT completion. However, there is a need for stronger evidence in older child and adolescent TB contacts to identify and support pragmatic and safe TPT implementation strategies. ■

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