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Isoniazid preventive therapy for children in sub-Saharan Africa

In 2017, an estimated 1 million children aged 15 years and under developed active tuberculosis disease and 239 000 children died from the disease.[1] In sub-Saharan Africa, tuberculosis in children remains a neglected issue and many children remain undiagnosed and untreated.[2] An estimated 1·7 billion adults and children worldwide have latent *Mycobacterium tuberculosis* infection (LTBI),[3] which can reactivate into active clinical disease during their lifetime. In children, risk factors for progression of existing LTBI to active tuberculosis disease or acquisition of new *M tuberculosis* infection include living with an adult with recently diagnosed sputum-smear pulmonary tuberculosis, malnutrition, HIV infection or other causes of immunocompromise, and being younger than 5 years old.[4]

It is well established that isoniazid preventive therapy (IPT) can reduce the overall risk of progression of LTBI to active tuberculosis disease in children by up to 59%.[5] IPT can also reduce the risk of active tuberculosis and death in children with newly diagnosed HIV not receiving antiretrovirals.[6] Therefore, testing and treatment of LTBI in child contacts to prevent progression of LTBI to active symptomatic disease is one of the ten priority indicators for monitoring the implementation of the WHO End TB Strategy, which has set targets at 90% or more LTBI contact investigation coverage and treatment.[7] Although several national and international guidelines for screening of LTBI and administering IPT have been developed, effective programmatic implementation of these by countries with high endemic tuberculosis has not been optimal. Disappointingly, in sub-Saharan Africa, 16% of children eligible for IPT were identified and given IPT in 2017,[1] and worldwide only 13% of eligible children are estimated to receive IPT.[8,9]

Despite the known effectiveness of IPT and its potential to contribute to reducing tuberculosis morbidity and mortality in children, uptake continues to remain at unacceptably low levels. A major step change in scaling up the implementation of IPT in sub-Saharan Africa is needed and will entail overcoming several obstacles (panel).[9–11]

These multifactorial, programmatic, community, and clinical limitations of implementing WHO LTBI IPT management recommendations require immediate, short, medium, and long-term plans. The plans should be supported with budgetary commitment to drastically change the current status quo and narrow the major gaps in IPT delivery, implementation, community acceptance, and treatment completion rates. Recent

Panel: **Obstacles to scaling up isoniazid preventive therapy (IPT) in sub-Saharan Africa**

- An absence of comprehensive and clear policies on IPT. Most countries do not have recommendations for screening, testing, and treatment for latent *Mycobacterium tuberculosis* infection (LTBI). Harmonisation of policy recommendations across regions is lacking.
- A lack of monitoring and evaluation systems for implementation of IPT across sub-Saharan Africa.
- Community-based and community-driven approaches for identifying children exposed to adults with active tuberculosis, and provision of easy access to care have not been forthcoming.
- Generic issues exist related to local cultural context, community knowledge, attitude, and anxieties towards any public health preventive interventions due to non-appreciation of the benefits of IPT.
- Parents, community leaders, and health-care workers might object to healthy children taking isoniazid, which has adverse side-effects and could be harmful. The benefit versus risk of the treatment are currently not well communicated or appreciated.
- LTBI service providers, parents, guardians, and children face numerous operational obstacles due to the lengthy treatment period of several months, travel cost and time, clinic schedules, and clinic waiting times, which discourage acceptance and results in poor adherence and non-completion of IPT.
- Programmatic issues include a lack of prioritisation of household contact management by governments and national tuberculosis control programmes, insufficient resources or budgets for implementation, inadequate isoniazid procurement and interrupted supply, knowledge gaps among caregivers and health-care workers, inadequate staffing, and stigma.
- Although short-term efficacy of IPT has been established, the long-term benefits of IPT are unknown. In sub-Saharan Africa, the high rates of adult pulmonary tuberculosis sustain *M tuberculosis* transmission in the community and household, increasing the likelihood of *M tuberculosis* reinfection in children, possibly reversing any long-term benefit of IPT. Health-care workers continue to experience several clinical management conundrums. Distinguishing between LTBI, subclinical tuberculosis, and active tuberculosis disease is not possible using current WHO approved LTBI or active tuberculosis diagnostic tests. An urgent need exists for development of a specific LTBI diagnostic test or biomarker.
- It is not possible to identify LTBI due to drug-resistant *M tuberculosis* strains, and inadvertant monodrug treatment for drug-resistant tuberculosis or sub-clinical tuberculosis disease is unavoidable. Implementation of IPT could worsen the growing problem of drug-resistant tuberculosis in Africa. Difficulty in obtaining *M tuberculosis* isolates from people with LTBI and defining their drug sensitivity patterns remains a vexatious issue.
- Insufficient investment in operational research to provide a scientific evidence base for optimal service delivery within the African context.

scientific and political developments provide renewed hope and opportunities for tackling some of the obstacles and improve the management of LTBI in children in sub-Saharan Africa. A mathematical modelling study[12] has shown that one of the most effective ways of identifying children with LTBI is through household contact management investigations.[12] The latest WHO guidelines for treatment of LTBI[13] are comprehensive and universally applicable. The guidelines clarify and simplify issues related to who to screen, which tests, and what treatment regimens to use under available resources to have a wider public health impact. These guidelines pave the way for sub-Saharan Africa to progress with comprehensive and clear policies on IPT, taking forward the changes in the WHO guidelines on tuberculosis preventive treatment services for high tuberculosis burden settings, including shorter preventive treatment regimens. The guidelines strongly recommend screening and treatment for LTBI in children who are household contacts of people with active pulmonary tuberculosis. Clarifying which test to use, WHO recommends either a tuberculin skin test or interferon-γ release assay, or initial screening with a clinical algorithm at primary care health facilities where these tests might not be available. Specific recommendations are also made for children infected with HIV.[13] Shorter LTBI treatment regimens are associated with better adherence and higher treatment completion rates, and thus two regimens seem appropriate for sub-Saharan Africa settings. Isoniazid (given with pyridoxine) to be taken once a day for 6 months rather than 9 months might be more acceptable by parents, communities, and health-care workers. Isoniazid plus rifampicin for 3 months, is recommended for children aged less than 15 years as an alternative to isoniazid alone. A 12-week course of rifapentine combined with isoniazid taken once a week for 12 weeks is another alternative, although it has cost and operational challenges.

All sub-Saharan African countries signed the political declaration arising from the historic UN High Level Meeting on tuberculosis held in New York, USA, on Sept 26, 2018.[14] The declaration included commitment to providing preventive treatment to 30 million individuals with LTBI by 2022. In light of this commitment, it is now imperative for sub-Saharan African countries to play an essential role in changing the status quo and take leadership of programmatic management and implementation of LTBI, establishing regional monitoring and evaluation systems for IPT implementation.

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Spotting the old foe—revisiting the case definition for TB

Disease case definitions are important instruments for clinical care, interventional research, and surveillance. Therefore, it is concerning that the current case definitions for tuberculosis remain underscored by the classic paradigm of binary states of latent infection and active disease, with a stepwise, linear transition under which symptoms, bacteriological positivity, and disease pathology are assumed to emerge broadly together (figure, A).[1] This assumption has resulted in a reliance on symptom screening to distinguish these two states. However, in recent prevalence surveys, 40–79% of bacteriologically positive tuberculosis occurs in the absence of patient-recognised tuberculosis symptoms.[2] Rather than explicitly addressing this discordance, tuberculosis case definitions are often ambiguous regarding tuberculosis symptoms, or internally inconsistent.

We propose a new perspective on the case definition of pulmonary tuberculosis, one that resolves the current ambiguity of tuberculosis symptoms and recognises the presence and dynamics of subclinical tuberculosis.[3] Under this paradigm, individuals with subclinical tuberculosis, also referred to as the walking well, have *Mycobacterium tuberculosis* bacteriologically positive pulmonary lesions and are thus able to transmit *M tuberculosis* intermittently or persistently through symptoms they are not aware of, do not acknowledge, or attribute to alternative conditions (figure, B).[4] Crucially, some of these individuals might never advance to clinical tuberculosis disease, but instead persist at the subclinical level for an unknown period, or regress and self-cure (figure, C).[5]

Allowing for case definitions that recognise distinct disease phenotypes has wide precedent. For example, both HIV and malaria have well established definitions for infectious, but not clinically ill individuals (eg, people living with HIV[6] and (sub)patent malaria infections[7]). In tuberculosis, the implications of current practices