

Comment for World TB Day - Lancet Respiratory Medicine

For the attention of Dr Laura Feetham and Dr Emma Grainger -Editors

**Title:**

Isoniazid Preventive therapy for children in sub-Saharan Africa - obstacles and opportunities for universal coverage

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**Word count:** 1,120 words

**References:** 14

**Declarations:** Authors declare no conflicts of interest

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In 2017, an estimated 1.0 million children ( $\leq 15$ y) developed active TB disease and 239,000 children died from TB in 2017.<sup>1</sup> In sub-Saharan Africa TB in children remains a neglected issue and many children remain undiagnosed and untreated.<sup>2</sup> An estimated 1.7 billion adults and children worldwide have Latent *Mycobacterium tuberculosis* (*M.tb*) infection (LTBI)<sup>3</sup> which may re-activate into active clinical disease during their lifetime. In children, risk factors identified for progression of existing LTBI to active TB disease or acquisition of new *M.tb* infection include living with an adult with recently diagnosed sputum-smear pulmonary TB, malnutrition, HIV infection or other causes of immunocompromise, and being less than 5 years old.<sup>4</sup>

It is well established that isoniazid preventive therapy (IPT) can substantially reduce the risk of progression of LTBI to active TB disease in children by 50% or more.<sup>5</sup> IPT can also reduce the risk of active TB and death in children not receiving ARVs with newly diagnosed HIV.<sup>6</sup> Thus testing and treatment of LTBI in child contacts to prevent progression of LTBI to active symptomatic disease is one of the priority 10 indicators for monitoring the implementation of WHO End-TB strategy which has set targets at  $\geq 90\%$ .<sup>7</sup> Whilst several national and international guidelines for screening of LTBI and administering IPT have been developed over the years, effective programmatic implementation of these by high TB endemic countries has not been optimal. Disappointingly, in sub-Saharan Africa (SAA) 16% of children eligible for IPT were identified and given IPT in 2017<sup>1</sup> and worldwide only 13% of eligible children are estimated to receive IPT.<sup>8,9</sup>

Despite the known effectiveness of IPT and its potential to contribute to reducing TB morbidity and mortality in children, the uptake continues to remain at unacceptable levels. A major step-up change in scaling up the implementation of IPT in sub-Saharan Africa is needed and will require several major obstacles to be overcome.<sup>9-11</sup>

*First*, there are absence of comprehensive clear policies on IPT. Most countries do not have recommendations for screening, testing and treatment for LTBI and there is lack of harmonization of policy recommendations across countries and regions.

*Second*, is the lack of monitoring and evaluation system(s) for implementation of IPT across SSA.

*Third*, community-based and community-driven approaches for identifying children exposed to adults with active TB, and provision of easy access to care have not been forthcoming.

*Fourth*, are generic issues related to local cultural context, community knowledge, attitude and anxieties towards any public health preventive interventions due to non-appreciation of the benefits.

*Fifth*, there are parental, community and healthcare worker objections to healthy children taking INH which has adverse side effects and may be harmful. The benefit versus risk is not well communicated or appreciated.

*Sixth*, LTBI service providers, parents, guardians and children face numerous operational obstacles of 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.

*Seventh*, programmatic issues of lack of prioritization of household contact management (HCM) by governments and national TB control programs, insufficient supply of implementation tools, inadequate INH procurement and interrupted supply, knowledge gaps among caregivers and HCWs, inadequate staffing and stigma.

*Eighth*, whilst short-term efficacy of IPT has been proven, the long-term benefits of IPT are unknown. In SSA the high rates of adult pulmonary TB sustains *M.tb* transmission in the community and household, increasing the likelihood of *M.tb* reinfection in children, possibly reversing any long-term benefit of IPT.

*Ninth*, healthcare workers continue to experience several clinical management conundrums. Distinguishing between LTBI, subclinical TB and active TB disease is not possible using current WHO approved LTBI or active TB diagnostic tests. An urgent need exists for development of a specific LTBI diagnostic test or biomarker. Furthermore, it is not possible to identify LTBI due to drug resistant *M.tb* strains, how to avoid inadvertent mono-drug treatment for subclinical TB or drug resistant TB and whether implementation of IPT will worsen the growing problem of drug resistant TB in Africa? Access to *M.tb* isolates from persons with LTBI and defining their drug sensitivity patterns remains a vexed issue.

*Tenth*, there has been scanty investment into operational research to provide a scientific evidence base for optimal service delivery within the African context.

These multifactorial programmatic, community and clinical limitations of implementing WHO LTBI IPT management recommendations requires immediate, short, medium and long-term plans backed-up 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 scientific and political developments provide renewed

hope and opportunities for tackling some of these obstacles and improve the management of LTBI in children in SSA. Recent operational studies confirm that one of the most effective ways of identifying children with LTBI and is through household contact management (HCM) investigations.<sup>12</sup> The latest WHO guidelines for treatment of LTBI<sup>13</sup> are comprehensive and universally applicable. They now 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 pave the way for SSA to take forward comprehensive clear policies on IPT taking forward the changes in the WHO guidelines on TB preventive treatment services for high TB burden settings, including shorter preventive treatment regimen. They strongly recommend screening and treatment for LTBI in children who are household contacts of persons with active pulmonary TB. Clarifying which test to use, WHO recommends either a tuberculin skin test (TST) or interferon-gamma release assay (IGRA) or initial screening with clinical algorithm at first level health facilities where these tests may not be available. Specific recommendations are also made for HIV-infected children.<sup>13</sup> Shorter LTBI treatment regimens are associated with better adherence and higher treatment completion rates and thus two regimens seem appropriate for SSA settings. Isoniazid or INH (given with pyridoxine) to be taken daily for 6 months rather than 9 months may be more acceptable by parents, communities and healthcare workers. Isoniazid plus rifampicin for 3 months (3RH), is recommended for children <15y as alternative to isoniazid alone. A 12-week course of rifapentine combined with isoniazid (3HP) taken once a week for 12 weeks is another alternative although it has cost and operational challenges.

All Sub-Saharan countries signed up to the priority commitment in the political declaration arising from the historic United Nations High Level Meeting on TB held in October 2018<sup>14</sup> for providing preventive treatment to 30 million individuals with LTBI by 2022. In light of this it is now imperative for SSA countries to play a critical role in changing the status quo and take leadership of programmatic management and implementation of LTBI and establish regional monitoring and evaluation systems for IPT implementation.

## References

1. World Health Organization. Global Tuberculosis Report 2018. Geneva: WHO; 2018. [https://www.who.int/tb/publications/global\\_report/en/](https://www.who.int/tb/publications/global_report/en/) -accessed Decmebr 5<sup>th</sup> 2018.
2. Bates M, Shibemba A, Mudenda V, Chimoga C, Tembo J, Kabwe M, Chilufya M, Hoelscher M, Maeurer M, Sinyangwe S, Mwaba P, Kapata N, Zumla A. Burden of respiratory tract

infections at post mortem in Zambian children. *BMC Med.* 2016 Jul 1;14:99. doi: 10.1186/s12916-016-0645-z

3. Houben RM, Dodd PJ. The global burden of latent tuberculosis infection: a re-estimation using mathematical modelling. *PLoS Med.* 2016;13(10):e1002152 (<https://www.ncbi.nlm.nih.gov/pubmed/27780211>, accessed 30 Nov 2018).

4. WHO 2018. Roadmap towards ending TB in children and adolescents, second edition. Geneva: World Health Organization; 2018 Roadmap towards ending TB in children and adolescents, second edition ISBN 978-92-4-151479-8

5. Ayieko J, Abuogi L, Simchowitz B, Bukusi EA, Smith AH, Reingold A. Efficacy of isoniazid prophylactic therapy in prevention of tuberculosis in children: a meta-analysis. *BMC Infect Dis.* 2014 Feb 20;14:91.

6. Zunza M, Gray DM, Young T, Cotton M, Zar HJ. Isoniazid for preventing tuberculosis in HIV-infected children. *Cochrane Database Syst Rev.* 2017 Aug 29;8:CD006418. doi: 10.1002/14651858.CD006418.pub3.

7. WHO End TB Strategy: global strategy and targets for tuberculosis prevention, care and control after 2015. Geneva: WHO; 2015 ([http://www.who.int/tb/post2015\\_strategy/en/](http://www.who.int/tb/post2015_strategy/en/), accessed 30 July 2018).

8. Szkwarko D, Hirsch-Moverman Y, Du Plessis L, Du Preez K, Carr C, Mandalakas AM. Child contact management in high tuberculosis burden countries: a mixed-methods systematic review. *PLoS One.* 2017;12:e0182185

9. Rodriguez CA, Sasse S, Yuengling KA, Azzawi S, Becerra MC, Yuen CM. A systematic review of national policies for the management of persons exposed to tuberculosis. *Int J Tuberc Lung Dis.* 2017;21:935-940

10. Jagger A, Reiter-Karam S, Hamada Y, Getahun H. Barriers to scale-up of tuberculosis preventive treatment include the absence of national policies and a lack of monitoring and evaluation systems National policies on the management of latent tuberculosis infection: review of 98 countries. *Bull World Health Organ.* 2018 Mar 1;96(3):173-184F. doi: 10.2471/BLT.17.199414

11. Luabeya KK, Tameris MD, Geldenhuys HD, Mulenga H, Van Schalkwyk A, Hughes EJ, Toefey A, Scriba TJ, Hussey G, Mahomed H, McShane H, Landry B, Hanekom WA, Hatherill M. Risk of Disease After Isoniazid Preventive Therapy for Mycobacterium tuberculosis Exposure in Young HIV-uninfected Children. *Pediatr Infect Dis J.* 2015 Nov;34(11):1218-22.

12. Dodd PJ, Yuen CM, Becerra MC, Revill P, Jenkins HE, Seddon JA. Potential effect of household contact management on childhood tuberculosis: a mathematical modelling study. *Lancet Glob Health.* 2018 Dec;6(12):e1329-e1338. doi: 10.1016/S2214-109X(18)30401-7.

13. World Health Organization; Geneva: 2018. Latent TB infection: updated and consolidated guidelines for programmatic management. <http://www.who.int/tb/publications/2018/latent-tuberculosis-infection/en/>

14. Marais B, Zumla A. Advancing global tuberculosis control after the UNGA-HLM. *Lancet.* 2018 Sep 29;392(10153):1096-1097.