Title

"Yes! We can end TB," but remember the sequelae in children

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As we mark World Tuberculosis Day on March 24, 2024, under the theme of *"Yes! We can end TB"*, we must remember that achieving zero cases and deaths is only one aspect of the battle against this tenacious disease.[1] To combat this disease effectively, we need a more comprehensive approach that includes every stage of the tuberculosis journey, from pre-treatment to life after tuberculosis.[2] This continuum of care, which incorporates post-tuberculosis assessment and care (figure), is essential to ensure that tuberculosis survivors, especially children and adolescents, can thrive without experiencing debilitating sequelae.[3]

Although there has been significant progress in the fight against tuberculosis, children and adolescents still bear a disproportionate burden of the disease. This vulnerable population accounted for an estimated 12% of new cases and 16% of all tuberculosis deaths in 2022.[4] Diagnosing tuberculosis in children remains a challenge.[1] Furthermore, many children who are eligible for preventive treatment do not receive it.[4] Even those children and adolescents who seem to recover from the disease are at risk of life-long consequences, including respiratory impairment and increased risk of non-communicable diseases later in life.[5-7] These post-tuberculosis sequelae, which are often ignored, can significantly impact their physical, social, and economic well-being.[8]

Emerging scientific evidence has revealed concerning findings about post-tuberculosis lung disease (PTLD) in children and adolescents.[6, 7, 9] According to these studies, even after being successfully treated, children and adolescents may still develop chronic wheezing, cough, impaired linear growth, reduced lung function and health-related quality of life.

Tuberculosis manifests differently in various paediatric age groups, suggesting that unique PTLD phenotypes may exist, with each group requiring tailored approaches for accurate diagnosis and effective intervention.[5, 8] Additionally, the lack of biomarkers presents a significant challenge to diagnosis and makes it difficult to compare research studies.[5] Unfortunately, we do not have a universal definition for PTLD, agreed-upon measurement tools, or the optimal timing for assessments, all of which significantly impede our understanding and management of this condition in children and adolescents.

At the first International Post-Tuberculosis Symposium held in Stellenbosch in 2019, a research definition for paediatric PTLD was proposed and later updated in 2023.[5, 10] Although this development offers some hope, it remains uncertain how the definition will be practically applied in research and clinical settings. There are still many unanswered questions about paediatric PTLD. For instance, how do we define it effectively for different age groups, considering their unique vulnerabilities and presentations? What parameters should be measured, and which reference ranges for normality should be used? When and how frequently

should these assessments be conducted to capture the dynamic nature of this condition accurately? These questions demonstrate that we have an incomplete understanding of paediatric PTLD and its impact on the lives of children and adolescents.[8]

Advocating for childhood and adolescent tuberculosis survivors is essential because they have developing lungs and live longer with the sequelae and, therefore, have an increased likelihood of long-term non-communicable disease.[11] While primary prevention strategies to help children and adolescents avoid contracting tuberculosis are crucial, increasing funding for post-tuberculosis research is also necessary to bridge the knowledge gap.

Unfortunately, childhood tuberculosis research continues to face a significant funding gap. In 2022, only a portion of the $2 billion investment target needed for tuberculosis research was reached.[12] Even with this considerable shortfall in funding for tuberculosis research and development globally, less than 10% of annual funding investments for tuberculosis research are devoted to children and adolescents.[13] This inequity in financing childhood tuberculosis research needs to be addressed urgently. The recent NIH call for proposals that focus on characterising PTLD in individuals living with HIV is a positive step.[14] Still, we need sustained and expanded funding to refine definitions, develop standardised tools, and identify risk factors for specific phenotypes. This investment will pave the way for the development of targeted interventions that address the unique needs of children and adolescents suffering from PTLD.

As we mark World Tuberculosis Day 2024, let us take a moment to acknowledge the progress that has been made in the fight against this disease. However, we must also remember there is still a long way to go. Children and adolescents are often silent sufferers of the lingering effects of tuberculosis, and they deserve our unwavering attention and dedicated action. By prioritising research on paediatric post-tuberculosis morbidity, bridging the funding gap, and advocating for a continuum of care that extends beyond diagnosis and treatment, we can truly fulfil the promise of World TB Day – a future where every young person, tuberculosis survivor or not, can breathe freely and thrive.

References

1. World Health Organization. Roadmap towards Ending TB in Children and Adolescents 2023. Available from: https://www.who.int/publications/i/item/9789240084254.

2. Subbaraman R, Jhaveri T, Nathavitharana RR. Closing gaps in the tuberculosis care cascade: an action-oriented research agenda. Journal of Clinical Tuberculosis and Other Mycobacterial Diseases. 2020;19:100144

3. Schoeman I, Sifumba Z. Tuberculosis care does not end at treatment completion; a perspective from tuberculosis survivors. The Lancet Infectious Diseases. 2021;21(7):896-7

4. World Health Organization. Global tuberculosis report 2023 2023. Available from: https://www.who.int/teams/global-tuberculosis-programme/tb-reports/global-tuberculosis-report-2023.

5. Allwood BW, van der Zalm MM, Amaral AFS, Byrne A, Datta S, Egere U, et al. Post-tuberculosis lung health: perspectives from the First International Symposium. The International Journal of Tuberculosis and Lung Disease. 2020;24(8):820-8

6. Nkereuwem E, Agbla S, Sallahdeen A, Owolabi O, Sillah AK, Genekah M, et al. Reduced lung function and health-related quality of life after treatment for pulmonary tuberculosis in Gambian children: a cross-sectional comparative study. Thorax. 2023 2023-3;78:281-7

7. van der Zalm MM, Jongen VW, Swanepoel R, Zimri K, Allwood B, Palmer M, et al. Impaired lung function in adolescents with pulmonary tuberculosis during treatment and following treatment completion. eClinicalMedicine. 2024 2024-1;67

8. Allwood BW, Byrne A, Meghji J, Rachow A, van der Zalm MM, Schoch OD. Post-Tuberculosis Lung Disease: Clinical Review of an Under-Recognised Global Challenge. Respiration. 2021;100(8):751-63

9. Martinez L, Gray DM, Botha M, Nel M, Chaya S, Jacobs C, et al. The Long-Term Impact of Early-Life Tuberculosis Disease on Child Health: A Prospective Birth Cohort Study. American Journal of Respiratory and Critical Care Medicine. 2023 2023-4-15;207:1080-8

10. Allwood BW, Nightingale R, Agbota G, Auld S, Bisson P, Byrne A, et al. Perspectives from the 2nd International Post-Tuberculosis Symposium: mobilising advocacy and research for improved outcomes. The International Journal of Tuberculosis and Lung Disease. 2024;In press

11. Nkereuwem E, Togun T, Kampmann B. Making a case for investing in post-tuberculosis lung health in children. The Lancet Respiratory Medicine. 2022;10(6):536-7

12. Stop TB Partnership. Tuberculosis Research Funding Trends, 2005–2022 2023. Available from: https://www.stoptb.org/advocate-to-endtb/tuberculosis-research-funding-trends-2005-2022.

13. McKenna L, Sari AH, Mane S, Scardigli A, Brigden G, Rouzier V, et al. Pediatric Tuberculosis Research and Development: Progress, Priorities and Funding Opportunities. Pathogens. 2022;11(2):128

14. Funding to Characterize Post-Tuberculosis Lung Disease in HIV-Infected Individuals [cited 2024 22 February]. Available from: https://www.niaid.nih.gov/grants-contracts/characterize-post-tuberculosis-lung-disease.

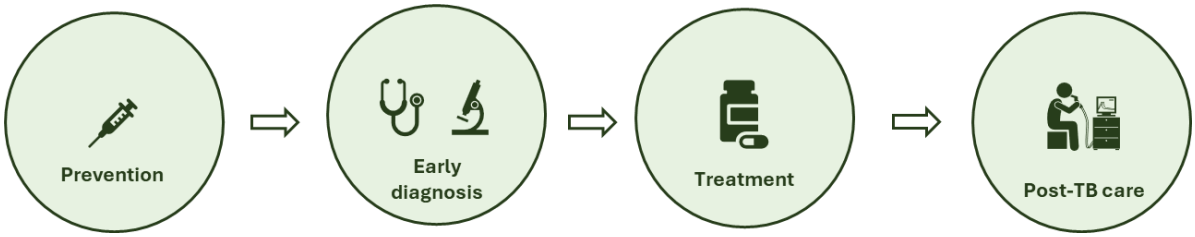

Figure: Proposed continuum of care for childhood and adolescent tuberculosis from disease prevention to post-tuberculosis care