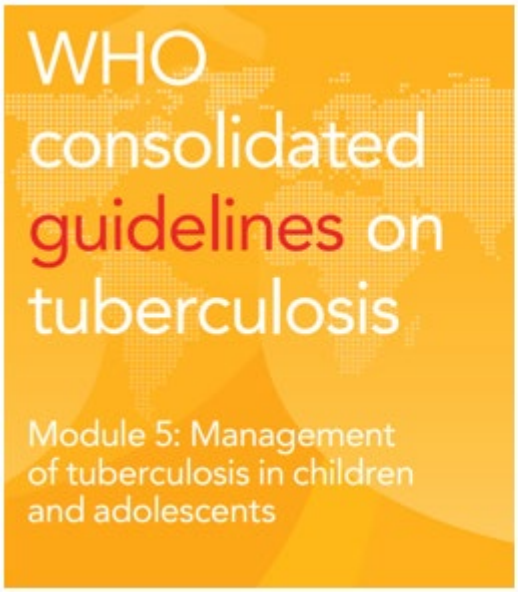
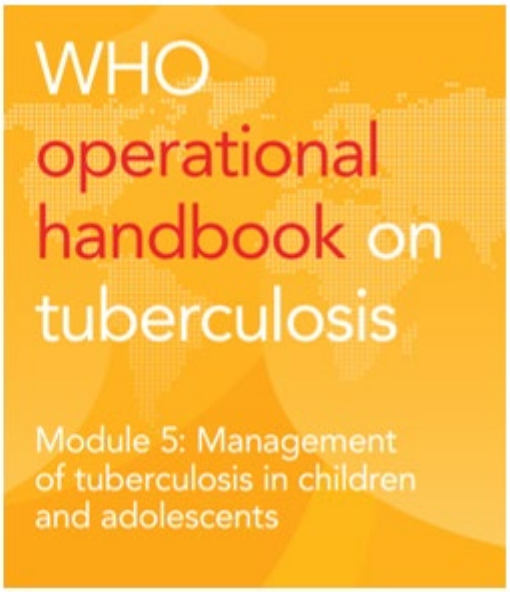
Title of the Impact Case Study: Research from the Desmond Tutu TB Centre at Stellenbosch University informs changes to WHO guidelines for the management of tuberculosis in children and adolescents globally.

Submitting University: Stellenbosch University

Summary of the impact:
In 2022 the World Health Organization (WHO) released their updated guidelines and operational handbook for the management of tuberculosis in children and adolescents. Of the eight new recommendations in these guidelines, four were directly informed by data generated by the multi-disciplinary team of researchers at the Desmond Tutu TB Centre (DTTC). Additionally a chapter on post-TB health was included in the handbook for the first time, an effort which was led by clinicians from DTTC in collaboration with Stellenbosch University colleagues, and a review to contextualise the WHO recommendations was also supported by researchers in the DTTC. These guidelines have global impact with the potential to increase the number of children and adolescents identified, diagnosed and successfully treated for tuberculosis and to support them to access treatment regimens that are acceptable, can be given at home, taken for a shorter duration and with fewer side-effects.





Underpinning academic work:
The DTTC is an academic research centre in the Department of Paediatrics and Child Health, Faculty of Medicine and Health Sciences, Cape Town, South Africa, established in 2003. In 2004, Archbishop Emeritus Desmond Tutu, who suffered from tuberculosis (TB) as a child, became its patron and the centre was formally named. The DTTC works closely with clinical colleagues in the Tygerberg Children's Hospital and the Department of Paediatrics and Child Health at Stellenbosch University and much of the research carried out by the DTTC is undertaken collaboratively with these clinical colleagues. The academic work underpinning the impact are outlined below:

1. *Diagnosis of TB in children.* The diagnosis of TB in children can be challenging due to the non-specific symptoms and signs of TB in childhood, as well as the difficulties in collecting respiratory specimens for laboratory evaluation. Researchers at DTTC, led by James Seddon, conducted an individual patient analysis of nearly 5,000 children evaluated for TB and developed a data-driven clinical treatment decision algorithm to help front-line health workers. (1)
2. *Shortened treatment is now possible with children with TB.* Most children with TB have a lower load of TB bacteria in their bodies than adults and it has always been considered that they may be able to be treated for a shorter period than the standard 6 months. Shorter treatment is easier for families and cheaper for TB programs. The SHINE trial found that treatment for 4 months was as good as treatment for 6 months in children with non-severe TB. As well as contributing towards the

development of the SHINE protocol and trial methods, DTTC enrolled 315 children on the SHINE trial. The trial at DTTC was led by Anneke Hesseling, Marieke van der Zalm and Megan Palmer. (2)

3. *New drugs for drug-resistant TB pave the way for access to child-friendly effective and safe regimens.* Two new drugs, bedaquiline and delamanid have recently been developed and have revolutionised the treatment of multidrug-resistant (MDR) TB in adults. However, there remained uncertainty around the correct dosage to use in children and the safety in this population. Investigators at the DTTC, led by Anneke Hesseling and Tony Garcia-Prats, carried out an individual patient systematic review and meta-analysis to evaluate the impact of these two drugs on treatment. DTTC also led a several clinical trials in children with MDR-TB that evaluated the drug dosages and safety of these two drugs and found the drugs safe and effective in children of all ages. (3)
4. *Adolescent TB.* Individuals 10-19 years of age have particular health needs and are frequently neglected by health programmes and little research has been conducted in this group. A team of adolescent TB experts (including several from DTTC) carried out an evidence review to better understand how adolescents with TB or eligible for TB preventive treatment be optimally engaged in care. (5)
5. *Post TB health and well-being.* Awareness of the consequences of TB disease in children and adolescents that go beyond survival and completion of treatment has increased. Besides the assignment of a mutually exclusive treatment outcome at the end of treatment, follow-up and care need to go beyond the conclusion of TB treatment. Improved data on post-TB health is important to increase awareness of the long-term consequences of TB and provide evidence-based interventions to improve post-TB health and to better plan for the care and support of affected children, adolescents and their families. Related to this, a new chapter on post-TB health was added in the WHO handbook and describes practical guidance for the assessment and management of post-TB health in children and adolescents. This was written by DTTC researchers in collaboration with colleagues from Stellenbosch University.

Narrative description of the impact:

In 2022, the World Health Organization (WHO) released their updated guidelines and operational handbook for the management of tuberculosis in children and adolescents (6,7). Of the eight new recommendations in these guidelines, four were directly informed by data generated by the multi-disciplinary team of researchers at the DTTC. Two additional background questions to contextualise the recommendations were also addressed, one of which included several members of the DTTC. Also, for the first-time post-TB health and well-being was included as a separate chapter in the operational handbook, which was led by researchers and clinicians from DTTC and Stellenbosch University. These guidelines have global impact with the potential to increase the number of children identified, diagnosed and successfully treated for TB and to support children to access treatment regimens that can be given at home, taken for shorter and with less associated side-effects.

1. *In children with presumptive pulmonary TB attending health care facilities, integrated treatment decision algorithms may be used to diagnose pulmonary TB.* It is estimated that approximately 40% of children with TB do not access appropriate treatment, largely because they are not diagnosed. This new WHO recommendation will contribute towards closing this diagnostic gap and decreasing unnecessary morbidity and mortality in children with TB.

Articles

Development of treatment-decision algorithms for children evaluated for pulmonary tuberculosis: an individual participant data meta-analysis

Kenneth S Gunasekera, Olivier Marcy, Johanna Muñoz, Elisa Lopez-Varela, Moorine P Sekadde, Molly F Franke, Maryline Bonnet, Shakil Ahmed, Farhana Amanullah, Aliya Anwar, Orvalho Augusto, Rafaela Baroni Aurilio, Sayera Banu, Iraj Batool, Annemieke Brands, Kevin P Cain, Lucia Carratalà-Castro, Maxine Caws, Eleanor S Click, Lisa M Cranmer, Alberto L García-Basteiro, Anneke C Hesseling, Julie Huynh, Senjuti Kabir, Leonid Lecca, Anna Mandalakas, Fanxi Mavhunga, Aye Aye Myint, Kyaw Myo, Dorah Nampijja, Mark P Nicol, Patrick Onkiintza, Megan Palmer, Clemax Couto Sant'Anna, Sara Ahmed Siddiqui, Jonathan P Smith, Rinn Song, Nguyen Thuy Thuong Thuong, Vibol Ung, Marieke M van der Zalm, Sabine Verkuijl, Keri Viney, Elisabetta G Walters, Joshua L Warren, Heather J Zar, Ben J Marais, Stephen M Graham, Thomas P A Debray, Ted Cohen, James A Seddon

Summary

Background Many children with pulmonary tuberculosis remain undiagnosed and untreated with related high morbidity and mortality. Recent advances in childhood tuberculosis algorithm development have incorporated prediction modelling, but studies so far have been small and localised, with limited generalisability. We aimed to evaluate the performance of currently used diagnostic algorithms and to use prediction modelling to develop evidence-based algorithms to assist in tuberculosis treatment decision making for children presenting to primary health-care centres.

Methods For this meta-analysis, we identified individual participant data from a WHO public call for data on the management of tuberculosis in children and adolescents and referral from childhood tuberculosis experts. We included studies that prospectively recruited consecutive participants younger than 10 years attending health-care centres in countries with a high tuberculosis incidence for clinical evaluation of pulmonary tuberculosis. We collated individual participant data including clinical, bacteriological, and radiological information and a standardised reference classification of pulmonary tuberculosis. Using this dataset, we first retrospectively evaluated the performance of several existing treatment-decision algorithms. We then used the data to develop two multivariable prediction models that included features used in clinical evaluation of pulmonary tuberculosis—one with chest x-ray features and one without—and we investigated each model's generalisability using internal–external cross-validation. The parameter coefficient estimates of the two models were scaled into two scoring systems to classify tuberculosis with a prespecified sensitivity target. The two scoring systems were used to develop two pragmatic, treatment-decision algorithms for use in primary health-care settings.

Findings Of 4718 children from 13 studies from 12 countries, 1811 (38·4%) were classified as having pulmonary tuberculosis: 541 (29·9%) bacteriologically confirmed and 1270 (70·1%) unconfirmed. Existing treatment-decision algorithms had highly variable diagnostic performance. The scoring system derived from the prediction model that included clinical features and features from chest x-ray had a combined sensitivity of 0·86 [95% CI 0·68–0·94] and specificity of 0·37 [0·15–0·66] against a composite reference standard. The scoring system derived from the model that included only clinical features had a combined sensitivity of 0·84 [95% CI 0·66–0·93] and specificity of 0·30 [0·13–0·56] against a composite reference standard. The scoring system from each model was placed after triage steps, including assessment of illness acuity and risk of poor tuberculosis-related outcomes, to develop treatment-decision algorithms.

Interpretation We adopted an evidence-based approach to develop pragmatic algorithms to guide tuberculosis treatment decisions in children, irrespective of the resources locally available. This approach will empower health workers in primary health-care settings with high tuberculosis incidence and limited resources to initiate tuberculosis treatment in children to improve access to care and reduce tuberculosis-related mortality. These algorithms have been included in the operational handbook accompanying the latest WHO guidelines on the management of tuberculosis in children and adolescents. Future prospective evaluation of algorithms, including those developed in this work, is necessary to investigate clinical performance.

Funding WHO, US National Institutes of Health.

Copyright © 2023 World Health Organization. Published by Elsevier Ltd. All rights reserved. This is an Open Access article published under the CC BY 3.0 IGO license which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited. In any use of this article, there should be no suggestion that

Figure 1. Manuscript published in the *Lancet Child and Adolescent Health* journal describing the development of a data-driven treatment-decision algorithm for TB in children, led by DTTC investigator James Seddon, which informed WHO guidelines.

2. *In children and adolescents between 3 months and 16 years of age with non-severe TB (without suspicion or evidence of multidrug- or rifampicin-resistant TB (MDR/RR-TB), a 4-month treatment regimen (2HRZ(E)/2HR) should be used.* It is estimated that at least two thirds of children with TB have non-severe disease. The new WHO recommendation regarding treatment shortening will allow these children to be treated for 4 months instead of 6 months – this is easier for children and their caregivers and is more cost-effective for TB programs. Additionally, this recommendation paves the way for investigating even shorter treatment regimens in the future.

Figure 2. Children enrolled on the SHINE trial at the DTTC site. This trial generated crucial evidence to support TB treatment shortening in children.

3. *In children with MDR/RR-TB aged below 6 years, an all-oral treatment regimen containing bedaquiline may be used*. MDR/RR-TB is TB that is resistant to first-line TB drugs. Children with MDR/RR-TB have traditionally required treatment for longer (9-18 months), often with daily intramuscular injections that require hospital admission and separation from families. When a drug called bedaquiline is included in treatment regimens for MDR/RR-TB the treatment can be shorter and the injectables can be avoided but, until 2022 this drug was not available to children below the age of 6 years, due to lack of evidence. To facilitate this access, DTTC enrolled 40 of the 54 children on the IMPAACT 1108 trial, which generated data on the dosing and safety of bedaquiline in children, permitting bedaquiline to be included in WHO's recommended treatment regimens for children with MDR/RR-TB of all ages. This means that children with MDR/RR-TB can now be treated for shorter, with safe, effective, oral drugs and do not require hospitalisation. The protocol chair of this pivotal trial was Anneke Hesseling, director of DTTC. *In children with MDR/RR-TB aged below 3 years delamanid may be used as part of longer regimens*. Similarly to bedaquiline, delamanid is a newer TB drug that can be included in shorter, optimised treatment regimens for MDR/RR-TB but which remained inaccessible to children due to lack of data. DTTC implemented the first delamanid trial in children, helping to generate the necessary dosing and safety data to allow for the inclusion of this drug in the WHO recommendations (5).

Figure 3. adult 100 mg and novel paediatric 20 mg scored dispersible child-friendly 20 mg bedaquiline formulation

4. *Adolescent TB*. The final consensus statement included in the updated WHO guidelines, based on expert opinion from a team of experts (including several from DTTC), proposes nine interventions to reform current practices that may harm adolescent health and well-being, and nine interventions to establish high-quality adolescent-centred TB services. These recommendations will make TB care more accessible to adolescents, who have traditionally fallen in the gap between children and adults and who have specific needs. (6)

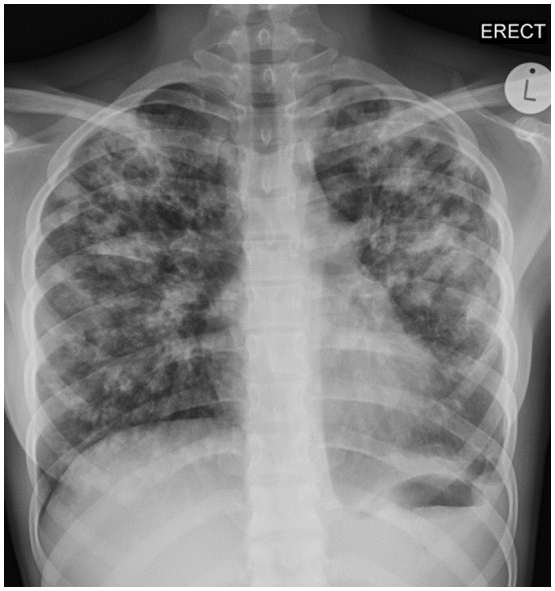


Figure 4. Typical chest x-ray from an adolescent with TB. Adolescents are a vulnerable and neglected population and the consensus statement related to their care in the updated WHO guidelines prioritises adolescent-centred TB services.

5. *Practical guidance for the assessment and management of post-TB health in children and adolescents with pulmonary TB, TB meningitis and osteo-articular TB*. This new chapter in the WHO handbook provides practical recommendations for the assessment of patients at the end of TB treatment, including timing and tools. This will contribute towards a better understanding of the burden of post-TB morbidity in children and facilitate appropriate follow-up and care for those at risk.

Evidence and sources to corroborate the impact:

1. WHO consolidated guidelines on tuberculosis. Module 5: management of tuberculosis in children and adolescents, 2022 update. Geneva: World Health Organization; 2022.
2. WHO operational handbook on tuberculosis. Module 5: management of tuberculosis in children and adolescents, 2022 update. Geneva: World Health Organization; 2022
3. Gunasekera KS et al. *Development of treatment-decision algorithms for children evaluated for pulmonary tuberculosis: an individual participant data meta-analysis*. Lancet Child Adolesc Health. 2023 May;7(5):336-346. doi: 10.1016/S2352-4642(23)00004-4. Epub 2023 Mar 13. PubMed PMID: 36924781; PubMed Central PMCID: PMC10127218.
4. Turkova A, Wills GA, Wobudeya E, Chabala C, Palmer M, Kinikar A, et al. *Shorter treatment for nonsevere tuberculosis in African and Indian children*. N Engl J Med. 2022;386(7).
5. Report of a WHO expert consultation on dosing to enable implementation of treatment recommendations in the WHO consolidated guidelines on the management of TB in children and adolescents. Geneva: World Health Organization; 2022. Licence: CC BY-NC-SA 3.0 IGO.
6. Allwood B, van der Zalm MM et al. Post-tuberculosis lung health: perspectives from the First International Symposium. Int J Tuberc Lung Dis. 2020 Aug. 24(8):820-828.doi: 10.5588/ijtld.20.0067. PMID 32912387

Signed off on behalf of the University by:

Maryke Hunter-Hüsselmann
Director: Research Information and Strategic Initiatives
Division for Research Development (DRD)
Stellenbosch University
Mh3@sun.ac.za

Date: 14 June 2024