Rapid communication on updated guidance on the management of tuberculosis in children and adolescents

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ISBN 978-92-4-003345-0 (electronic version)
ISBN 978-92-4-003346-7 (print version)

Background

Children and young adolescents (aged from 0 - 14 years; for monitoring and evaluation purposes collectively referred to as children[1]) represent approximately 12% of all tuberculosis (TB) patients globally, with 1.2 million children becoming ill with TB every year, and 230,000 estimated to have died of TB in 2019.[2] Between 25,000 and 32,000 children are estimated to develop multi-drug resistant TB (MDR-TB) every year.[3, 4] Over half of the children with TB are not diagnosed or are not reported. This case detection gap is largest in young children; 65% of children aged below 5 years of age are not detected. As well, only one third of household contacts aged below 5 who were eligible for TB preventive treatment (TPT) in 2019 received it.[2]

The political declaration of the 2018 United Nations General Assembly High Level Meeting on the Fight Against TB commits, among others, to diagnosing and treating 40 million people with TB, including 3.5 million children, and 1.5 million people with drug-resistant TB, including 115,000 children.[5] It also commits to providing at least 30 million people - including 4 million children under 5 years of age, 20 million other household contacts (including children over the age of 5 years) and 6 million people living with HIV (including children) - with TB preventive treatment by 2022.[5] In order to achieve these ambitious targets, there is an urgent need to improve prevention, diagnosis, treatment and care for children and adolescents with TB or at risk of developing it.

To support countries in responding to the challenges of TB, WHO's Global Tuberculosis Programme develops guidance on prevention, diagnosis, treatment, and care of people with TB, including for children and adolescents. The first edition of *Guidance for national tuberculosis programmes on the management of tuberculosis in children* was published in 2006, after which a *Rapid Advice on the treatment of tuberculosis in children* was released in 2010. In 2014, WHO published the second edition of the *Guidance for national tuberculosis programmes on the management of tuberculosis in children*. Since 2014, several recommendations pertaining to the management of TB in children and adolescents have been published in guidelines issued by WHO's Global Tuberculosis Programme.

Since the publication of the previous guidelines, critical gaps have been identified in diagnostic approaches for TB in children, the optimal duration of treatment for children with non-severe, drug-susceptible TB, treatment regimens for drug-resistant TB and TB meningitis, as well as optimal models of care for the delivery of child and adolescent TB services. In light of new evidence on these topics available to WHO's Global Tuberculosis Programme in 2021, and aligned with requests from Member States, WHO convened a Guideline Development Group (GDG) to examine the evidence in order to

[1] Children (aged 0-9 years) and young adolescents (aged 10-14 years) are referred to as children in this section based on historical surveillance definitions. However, in 2020, WHO's Global Tuberculosis Programme asked countries to report data on national notifications for more disaggregated age groups (0–4, 5–9, 10–14 and 15–19 years, compared with the previous groupings of 0–4 and 5–14 years.

[2] Global Tuberculosis Report 2020. 2020. Geneva, Switzerland: World Health Organization. Available at: https://www.who.int/tb/publications/global_report/en/

[3] Dodd PJ, Sismanidis C, Seddon JA. Global burden of drug-resistant tuberculosis in children: a mathematical modelling study. The Lancet Infectious Diseases. 2016;16(10):1193-201 (http://dx.doi.org/10.1016/S1473-3099(16)30132-3.

[4] Jenkins HE, Tolman AW, Yuen CM, Parr JB, Keshavjee S, Pérez-Vélez CM et al. Incidence of multidrug-resistant tuberculosis disease in children: systematic review and global estimates. The Lancet. 2014;383(9928):1572-9.

[5] Political declaration of the UN General-Assembly High-Level Meeting on the Fight Against Tuberculosis. https://www.who.int/publications/m/item/political-declaration-of-the-un-general-assembly-high-level-meeting-on-the-fight-against-tuberculosis

update the 2014 *Guidance for national tuberculosis programmes on the management of tuberculosis in children*. The GDG met in virtual sessions from 31 May to 17 June 2021 and proposed several new recommendations related to the management of TB in children and adolescents.[6]

Following on from the GDG meeting, the preparation of consolidated WHO guidelines on the management of TB in children and adolescents, including the new recommendations as well as existing recommendations and a related operational handbook are underway. Both documents are expected to be released by the end of the year and will become available on the WHO Global Tuberculosis Programme's knowledge sharing platform in *Module 5: Co-morbidities, vulnerable populations and people-centred care: Management of tuberculosis in children and adolescents.*

This Rapid Communication is being issued to help national TB programmes and other stakeholders prepare for the changes that will be introduced in the new consolidated WHO guidelines on the management of TB in children and adolescents. Full implementation of the recommendations will only be possible after the new guidance is published by WHO, as the guidelines and operational handbook will address a range of implementation considerations.

Key findings

Diagnostic approaches in children aged below 10 years

Integrated treatment decision algorithms

Various algorithms and scoring systems for the diagnosis of TB in children are currently in use, but these have not been systematically evaluated. To overcome the large case detection gap, especially in children under 10 years of age, evidence-based, pragmatic treatment decision algorithms are needed, ideally for different settings with varying access to diagnostic tests and chest radiography, as well as for children with co-morbidities, such as HIV infection. A review of individual patient data (IPD) from diagnostic evaluation studies (comprising 14 cohorts from 13 countries, with 4811 participants) was conducted to assess the sensitivity and specificity of existing treatment decision algorithms designed to detect pulmonary TB, which was defined according to a pre-specified clinical case definition.[7] Each of these algorithms was compared to an algorithm considered to align closest to the current standard of care for diagnosing TB in children.[8] The sensitivity of the algorithms ranged from 16% (95% CI: 9-27%) to 95% (95% CI: 88-98%) and specificity ranged from 9% (95% CI: 3-24%) to 89% (95% CI: 80-95%). Algorithms with a high sensitivity had a low specificity and vice versa. The standard of care algorithm had a sensitivity of 65% (95% CI: 52-76%) and a specificity of 64% (95% CI: 44-80%).

The use of Xpert Ultra in gastric aspirate and stool samples

The Xpert MTB/RIF Ultra cartridge (Cepheid, Sunnyvale, USA), hereafter referred to as Xpert Ultra, was developed as the next-generation assay to overcome the suboptimal sensitivity in smear-negative TB patients when using the Xpert MTB/RIF assay. Existing WHO recommendations support the use of the

[6]The focus population for this guideline is children and adolescents, defined as: A child is a person under 10 years of age (0-9 years); An adolescent is a person 10-19 years of age (inclusive).

[7] Graham SM, Cuevas LE, Jean-Philippe P, et al. Clinical Case Definitions for Classification of Intrathoracic Tuberculosis in Children: An Update. Clin Infect Dis. 2015 Oct 15;61Suppl 3(Suppl 3):S179-87. doi: 10.1093/cid/civ581

[8] The International Union Against Tuberculosis and Lung Disease. The Union's desk guide for diagnosis and management of TB in children. Third edition. 2016. Paris, France: The International Union Against Tuberculosis and Lung Disease.

Xpert Ultra assay in sputum and naso-pharyngeal aspirate samples in children for the diagnosis of TB and rifampicin resistance, in addition to the use of Xpert MTB/RIF cartridge (Cepheid, Sunnyvale, USA) in sputum, gastric aspirate, naso-pharyngeal aspirate and stool.[9] The diagnostic accuracy of Xpert Ultra in gastric aspirate and stool samples for the diagnosis of pulmonary TB and rifampicin resistance against a microbiological reference standard (solid or liquid culture) was assessed in a systematic review and meta-analysis. The review included six studies involving 659 participants for gastric aspirate samples and six studies involving 1278 participants for stool samples. Studies were from nine countries (including four high TB and five high TB-HIV burden countries). The sensitivity of Xpert Ultra for detection of *Mycobacterium tuberculosis* was 64% (95% CI: 48 to 77%) in gastric aspirate samples and 53% (95% CI: 35 to 70%) in stool samples. The specificity was 95% in gastric aspirate samples (95% CI: 84 to 99%) and 98% in stool (CI: 93 to 99%). The benefit of detecting rifampicin resistance using Xpert Ultra was extrapolated from adult data.

Treatment shortening in children and adolescents with non-severe tuberculosis

Evidence from the SHINE trial (Shorter Treatment for Minimal Tuberculosis in Children)[10] was reviewed by the GDG. The SHINE trial was an open-label treatment-shortening trial in children with non-severe, symptomatic, presumed drug-susceptible, smear-negative TB, conducted in Uganda, Zambia, South Africa and India. Children aged below 16 years were randomised to 16- versus 24-weeks of standard first-line anti-tuberculosis treatment, using WHO pre-qualified paediatric fixed-dose combination formulations composed of TB medicines in ratios that are aligned with WHO-recommended dosing for children. The primary efficacy outcomes reviewed by the GDG were death by 72 weeks, treatment failure and loss-to-follow-up. The primary safety outcome was grade ≥3 adverse events observed during treatment. The 4-month treatment regimen was non-inferior to the 6-month regimen for children treated for non-severe, smear-negative TB, presumed to be drug susceptible. Non-inferiority was consistent across all key analyses (including age groups, HIV status, type of TB and adherence).

The use of bedaquiline and delamanid for the treatment of rifampicin-resistant and multi-drug resistant TB in children

The use of bedaquiline in children aged below six years

Bedaquiline is a core component of both shorter all-oral regimens as well as longer regimens recommended by WHO for the treatment of multidrug- or rifampicin-resistant tuberculosis (MDR/RR-TB) for children aged 6 years and above.[11] The recommendations that apply to children are conditional and based on extrapolation of efficacy data in adults, in combination with pharmacokinetic (PK) and safety data from phase II trials for children aged 6-17 years.

[9] WHO consolidated guidelines on tuberculosis. Module 3: diagnosis – rapid diagnostics for tuberculosis detection. 2021 update. Geneva, Switzerland: World Health Organization. Available at: https://apps.who.int/iris/rest/bitstreams/1354562/retrieve

[10] Chabala C, Turkova A, Thomason MJ, et al. Shorter treatment for minimal tuberculosis (TB) in children (SHINE): a study protocol for a randomised controlled trial. Trials. 2018 Apr 19;19(1):237. doi: 10.1186/s13063-018-2608-5.

[11] WHO consolidated guidelines on tuberculosis. Module 4: treatment - drug-resistant tuberculosis treatment. 2020. Geneva: World Health Organization. Available at: https://apps.who.int/iris/rest/bitstreams/1280998/retrieve

Data from two phase II trials (TMC207-C211[12] and IMPAACT P1108[13]) were reviewed by the GDG. Data from TMC207-C211 corresponded to children aged 5 to 18 years and IMPAACT P1108 included children aged 0-6 years; therefore, the review of PK and safety data focused mainly on data from IMPAACT P1108. Although the sample size was small (N= 12), the GDG concluded that in children 0-6 years of age, there were no cardiac safety signals distinct from those reported in adults. Population PK models from both studies suggest that drug exposures observed in adults can be reached in most children receiving bedaquiline, although some dose modification may be necessary depending on the age and weight of the child.

In addition, data from a paediatric drug resistant (DR)-TB IPD were analysed descriptively (24,231 records from all six WHO regions, the majority from India and South Africa). Just under twenty thousand of these records were used for a matched analysis of treatment outcomes in children being treated for DR-TB. The analysis included 40 children aged below 6 years and 68 children aged 6-12 years who received bedaquiline. In the matched analysis, bedaquiline was significantly associated with shorter treatment duration and lower odds of injectable TB drug use. Although children aged less than six years receiving a bedaquiline based regimen had a lower proportion of successful treatment outcomes (75%) than those not receiving bedaquiline (84.1%), residual confounding (including confounding by indication) was thought to be likely.

The use of delamanid in children aged below three years

Since 2018, WHO has conditionally recommended the use of delamanid for the treatment of MDR/RR-TB patients aged 3 years or more on longer regimens, based on extrapolation of efficacy data in adults, and trial data on PK and safety in children.

Data were reviewed by the GDG from a phase I, open-label, age de-escalation trial designed to assess the PK, safety, and tolerability of delamanid administered twice daily for 10 days in children with MDR/RR-TB on treatment with an optimized background regimen (protocol 242-12-232) and from the corresponding open-label extension study (protocol 242-12-233).[14] Data from cohorts 1 (age 12-17 years), 2 (age 6-11 years), 3 (age 3-5 years) and 4 (age 0-2 years) for both protocols were reviewed. Exposures in the 0-2 year age group were lower than those of patients aged 3 years and older, necessitating a modelling/simulation approach to dosing. No cardiac safety signals distinct from those reported in adults were observed in children 0-2 years of age. However, these findings were based on the fact that children received lower drug exposures comparable to adults. Pharmacodynamic simulations suggested that clinically meaningful changes in QT (i.e., prolongation) would be unlikely in children under 3 years of age, even if higher doses were used to reach drug exposures comparable to

[12] A Phase II, Open-label, Multicenter, Single-arm Study to Evaluate the Pharmacokinetics, Safety, Tolerability and Anti-mycobacterial Activity of TMC207 in Combination With a Background Regimen of Multidrug Resistant Tuberculosis (MDR-TB) Medications for the Treatment of Children and Adolescents 0 Months to <18 Years of Age Who Have Confirmed or Probable Pulmonary MDR-TB. Available at: https://clinicaltrials.gov/ct2/show/NCT02354014

[13] Phase I/II, Open-Label, Single Arm Study to Evaluate the Pharmacokinetics, Safety and Tolerability, of Bedaquiline in Combination with optimized Individualized Multidrug-Resistant Tuberculosis (MDR-TB) on in HIV-Infected and HIV-Uninfected Infants, Children and Adolescents with MDR-TB Disease. Available at: https://www.impaactnetwork.org/studies/p1108

[14] A Phase I, Open-label, Multiple-dose, and Age De-escalation Trial to Assess the Pharmacokinetics, Safety and Tolerability of Delamanid (OPC 67683) in Pediatric Multidrug-resistant Tuberculosis Patients on Therapy With an Optimized Background Regimen of Anti-tuberculosis Drugs. Available at: https://clinicaltrials.gov/ct2/show/NCT01856634

A Phase II, Open-label, Multiple-dose Trial to Assess the Safety, Tolerability, Pharmacokinetics, and Efficacy of Delamanid (OPC-67683) in Pediatric Multidrug-resistant Tuberculosis Patients on Therapy With an Optimized Background Regimen of Anti-tuberculosis Drugs Over a 6-Month Treatment Period. Available at: https://clinicaltrials.gov/ct2/show/NCT01859923

those achieved in adults. The paediatric DR-TB IPD included only 7 children aged below 3 years treated with delamanid, 14 children aged 3-6 years, and 69 children aged 6-12 years. All 7 children aged below 3 years were successfully treated. The number of patients was insufficient for a matched analysis.

Treatment of TB meningitis in children and adolescents

TB meningitis (TBM) is the most serious and the second most common form of extrapulmonary TB in children and adolescents. Without timely diagnosis and treatment, TBM is fatal and treatment outcomes are often poor even when treatment is provided.[15] For children aged 0 to 10 years, WHO currently recommends a treatment regimen of twelve months, consisting of isoniazid, rifampicin, pyrazinamide, and ethambutol given daily for the first two months, followed by isoniazid and rifampicin given daily for ten additional months (2HRZE/10HR). The recommendation on the use of the 12-month regimen was based on a literature review conducted in 2009, largely based on non-randomized, non-comparative studies, which were not entered into GRADE (Grading of Recommendations, Assessment Development and Evaluation), given the lack of comparative data.[16]

A systematic review and meta-analysis was conducted to compare the effectiveness of a shorter, intensive regimen (using daily isoniazid, rifampicin, pyrazinamide, and ethionamide throughout for six months - 6HRZEto) versus the WHO-recommended twelve-month regimen. Dosing of isoniazid and rifampicin in the intervention regimen was slightly higher compared to the comparator regimen.[17] The shorter intensive regimen (3 studies, involving 724 participants) had a death rate of 8.0% (95% CI: 2-13%) versus 24.0% (95% CI: 18-32%) for the 12-month regimen (3 studies, 282 participants). Treatment success for the shorter intensive regimen was 83% (95% CI: 74-99%) versus 75% for the 12-month regimen (95% CI: 69-81%). Neurological sequelae occurred in 66% of survivors (95% CI: 55-75%) who received the shorter intensive regimen versus 36% (95% CI: 30-43%) in the 12-month regimen. Survival without neurological sequelae was 28% (95% CI: 20-41%) versus 48% (95% CI: 42-54%) for patients who received the shorter intensive regimen and the 12-month regimen, respectively. The GDG members noted the small number of studies and the potential for residual confounding.

Models of care for case detection and provision of TB preventive treatment in children and adolescents

Capacity for paediatric TB care is often highly centralized at the secondary or tertiary levels of the health