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

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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 care system, and children may present seriously ill at these services, after delays in accessing other services. Healthcare workers at the primary health care (PHC) level may have limited capacity and confidence in managing paediatric TB, although this is where most children with TB or at risk of TB initially seek care. In addition, TB screening is often not part of clinical algorithms for child health. There

[15] Chiang SS, Khan FA, Milstein MB, et al. Treatment outcomes of childhood tuberculous meningitis: a systematic review and meta-analysis. Lancet Infect Dis. 2014 Oct;14(10):947-57. doi: 10.1016/S1473-3099(14)70852-7. Epub 2014 Aug 6.
[16] WHO Rapid advice: Treatment of tuberculosis in children. Annex 1 - Evidence summary tables. 2010. Geneva, Switzerland: World Health Organization.
[17] Daily dosages used in the 6 month intensive regimen were: isoniazid 20 mg/kg (maximum 400 mg), rifampicin 20 mg/kg (maximum 600 mg), pyrazinamide 40 mg/kg (maximum 2000 mg), ethionamide 20mg/kg (maximum 750mg). Daily dosages used in the 12 month standard regimen are: isoniazid 7-15 mg/kg, rifampicin 10-20 mg/kg, pyrazinamide 30-40 mg/kg, ethambutol 15-25 mg/kg.

are many missed opportunities for contact tracing, TB prevention, TB detection and TB care and management, often because of weak integration of child and adolescent TB services with other programmes and services. Decentralization and family-centred, integrated care are highlighted as one of ten key actions in the 2018 *Roadmap Towards Ending TB in Children and Adolescents.*[18]

A systematic review was conducted to assess evidence on the impact of decentralized and family-centred, integrated approaches on case detection and the provision of TB preventive treatment (TPT). The evidence showed that combined health facility and community approaches (including improved diagnostic capacity in primary care and community outreach or screening services) increased the number of children and adolescents diagnosed with TB and decentralized services can increase the levels of TPT initiation. There was positive but limited evidence showing that different types of service integration increase TB case notifications in children and adolescents. Socio-economic support for families affected by TB was shown to improve TPT coverage and completion among children and adolescents as well.

Key updates

Based on the evidence reviewed and considering the discussions, deliberations and decisions of the GDG, the key updates for the upcoming TB guidelines will include the following points:

- In children aged below 10 years with presumptive pulmonary TB, treatment decision algorithms may be used to diagnose pulmonary TB. Bacteriological confirmation needs to be sought whenever possible, using available and recommended diagnostic tests and appropriate paediatric specimens. The choice of the treatment decision algorithm will depend on the specific population and available diagnostic tests. Practical guidance on treatment decision algorithms for different settings and populations will be included in the operational handbook which will be published alongside the guidelines.
- In children aged below 10 years with signs and symptoms of pulmonary TB, the latest evidence reviewed supports the use of Xpert MTB/ RIF Ultra in gastric aspirate or stool specimens as the initial diagnostic test for TB and the detection of rifampicin resistance, rather than smear microscopy/culture and phenotypic drug susceptibility testing (DST). This is in addition to sputum or naso-pharyngeal aspirate specimens, which are already recommended by WHO for Xpert Ultra testing, in the same population.[19]
- In children and adolescents under 16 years of age with non-severe, presumed drug-susceptible TB, a 4-month regimen (2HRZ(E)/2HR) should be used rather than the standard 6-month regimen (2HRZ(E)/4HR). Important implementation considerations were noted to determine eligibility for the shorter treatment regimen and will be described in the consolidated guidelines and in the operational handbook.
- In children with MDR/ RR-TB of all ages:

[18] Roadmap towards ending TB in children and adolescents: second edition. 2018. Geneva, Switzerland: World Health Organization. Available at: https://www.who.int/iris/bitstream/handle/10665/274374/9789241514668-eng.pdf

[19] WHO consolidated guidelines on tuberculosis. Module 3: diagnosis – rapid diagnostics for tuberculosis detection. . 2021. Geneva, Switzerland: World Health Organization. Available at: https://www.who.int/publications/i/item/9789240029415

    - Bedaquiline may be used as part of the shorter, all oral bedaquiline-containing regimen (conditionally recommended by WHO in 2020[20]) or as part of longer treatment regimens.
    - Delamanid may be used as part of longer treatment regimens.
    - These recommendations make it possible to design all-oral regimens for children of all ages.
- In children and adolescents with microbiologically confirmed or clinically diagnosed TB meningitis, presumed to be drug susceptible, a 6-month intensive regimen composed of 6HRZEto may be used as an alternative option to the WHO recommended 12-month regimen composed of 2HRZE/10HR. The existing strong recommendation for the 12-month regimen composed of 2HRZE/10HR remains in place.
- In high TB burden settings, decentralized and family-centred, integrated services may be implemented to improve TB case detection and the uptake of TB preventive treatment. In this context, decentralized services do not replace centralized or specialized child and adolescent TB services, rather, they complement them.

Next steps

- The updated recommendations will be released as the *WHO consolidated guidelines on tuberculosis: Module 5: Co-morbidities, vulnerable populations and people-centred care: Management of tuberculosis in children and adolescents* by the end of 2021. These guidelines will consolidate the updated recommendations and all relevant WHO guidance on the management of TB in children and adolescents and will include detailed results of the evidence that was reviewed, as well as GDG processes. The summary of findings and evidence to decision tables will be produced in conformity with the GRADE method and will be made available on the WHO Global Tuberculosis Programme website. The guidelines will be translated into French, Spanish and Russian.

- The guidelines will be accompanied by an operational handbook. This document will provide operational guidance on the new recommendations, including treatment decision algorithms for use in various settings and populations, eligibility criteria for shorter treatment regimens for children with non-severe, drug-susceptible TB, practical advice on building treatment regimens for children with MDR/RR- TB who are not eligible for shorter all-oral bedaquiline-containing regimens, and examples of models of care from various settings, among other topics. The content and structure of the operational handbook, as well as the preferred methods for dissemination of both the guidelines and the operational handbook will be informed by feedback collected by WHO's Global Tuberculosis Programme from National TB Programmes, technical partners and other key stakeholders through an online survey conducted between April and June 2021.

- WHO's Global Tuberculosis Programme will also undertake the following additional consultations to further inform the guidelines and operational handbook:
    - on dosing of bedaquiline and delamanid in younger age groups (0-6 and 0-3 years, respectively, taking into account the availability of child-friendly formulations), as well as the shorter intensive regimen for TB meningitis

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

- the classification of intrathoracic TB in children (currently intrathoracic lymphadenopathy is classified as extra-pulmonary TB).

- The release of the new guidelines and operational handbook will be followed by a series of WHO webinars for different regions to communicate the recommendations and implementation considerations. The new recommendations on the management of TB in children and adolescents will be included in the online knowledge sharing platform that WHO's Global Tuberculosis Programme has launched in June 2021, which provides access to all WHO guidelines, operational handbooks and eLearning tools.[21] The webinars and the online knowledge sharing platform will support countries to update their national guidelines, train staff, inform programme budgets and facilitate rapid transition to scale up interventions to improve the prevention, diagnosis and management of TB in children and adolescents.

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[21] WHO Global Tuberculosis Programme's knowledge sharing platform is accessible at: https://tbksp.org/en/home

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