WHO consolidated guidelines on tuberculosis

Module 5: Management of tuberculosis in children and adolescents

World Health Organization

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Abbreviations

AIDS	acquired immunodeficiency syndrome
ANC	antenatal care
ART	antiretroviral treatment
BCG	bacille Calmette-Guérin
C(A)LHIV	children (and adolescents) living with HIV infection
CHW	community health worker
CXR	chest X-ray or chest radiography
DR-TB	drug-resistant tuberculosis
DS-TB	drug-susceptible tuberculosis
DST	drug susceptibility testing
DTG	dolutegravir
E	ethambutol
EPTB	extrapulmonary TB
Eto	ethionamide
FDC	fixed-dose combination (medicines)
GDF	Stop TB Partnership Global Drug Facility
GDG	Guideline Development Group
GRADE	Grading of Recommendations Assessment, Development and Evaluation
GUV	germicidal ultraviolet
H	isoniazid
HEPA	high-efficiency particulate air
HIV	human immunodeficiency virus
KSP	Knowledge Sharing Platform
iCCM	integrated community case management
IGRA	interferon-gamma release assay
IMCI	integrated management of childhood illness
IPD	individual patient data (or dataset)
IPT	isoniazid preventive therapy
LAMP	loop-mediated isothermal amplification
LF-LAM	lateral flow lipoarabinomannan assay
LPA	line-probe assay
M	moxifloxacin
MDR-TB	multidrug-resistant tuberculosis
NAATs	nucleic acid amplification tests

NPA	nasopharyngeal aspirate
NRTIs	nucleoside reverse transcriptase inhibitors
NTLP	National TB and Leprosy Control Programme
NTP	National Tuberculosis Programme
OSF	optimized sucrose flotation
PHC	primary health care
PICO	Population, Intervention, Comparator and Outcomes
PK	pharmacokinetic(s)
PTB	pulmonary tuberculosis
R	rifampicin
RAL	raltegravir
RR-TB	rifampicin-resistant tuberculosis
SAGE	Strategic Advisory Group of Experts on Immunisation
SAM	severe acute malnutrition
SDGs	Sustainable Development Goals
SL-LPA	second-line line-probe assay
SOS	simple one step (stool processing method)
SPK	stool processing kit
TB	tuberculosis
TBM	tuberculous meningitis
TPT	TB preventive treatment
TST	tuberculin skin test
UNGA	United Nations General Assembly
US FDA	United States Food and Drug Administration
WHO	World Health Organization
XDR-TB	extensively drug-resistant tuberculosis
Z	pyrazinamide

Definitions

Unless otherwise specified, the terms defined here apply as used in this document. They may have different meanings in other contexts.

Active (tuberculosis) case-finding: Provider-initiated screening and testing in communities by mobile teams, often using mobile X-ray and rapid molecular tests. The term is sometimes used synonymously with "systematic screening".

Adherence: Extent to which a person's behaviour (e.g. taking medicines, following a particular diet, changing lifestyle) corresponds with agreed recommendations from a health care provider.

Advanced HIV disease: For adolescents and children aged 5 years and over, this is defined as a CD4 cell count below 200 cells/mm^3 or a WHO clinical stage 3 or 4 event at presentation for care. All children aged under 5 years living with HIV should be considered as having advanced disease at presentation.

Adverse event: Any untoward medical occurrence that may present in a person with TB during treatment with a pharmaceutical product but that does not necessarily have a causal relationship with the treatment.

Age groups: Unless stated otherwise in the text, the following definitions apply to the terms used in this document:

- Infant: aged under 1 year (12 months).
- Child: aged under 10 years.
    - Young child: aged under 5 years.
- Adolescent: aged 10–19 years (inclusive).
    - Young adolescent: aged 10–14 years.
    - Older adolescent: aged 15–19 years.
- Adult: aged 20 years or over.

Background HIV and tuberculosis drug resistance prevalence: Settings with high HIV prevalence are defined as those in which the HIV prevalence is 1% or higher among adult pregnant women, or 5% or higher among people with TB. WHO does not intend to establish thresholds for low, moderate or high levels of prevalence of isoniazid resistance. National TB programmes will establish definitions for their own countries.

Bacteriologically confirmed tuberculosis: TB diagnosed in a biological specimen by a WHO-approved rapid test such as Xpert® MTB/RIF or LF-LAM, smear microscopy or culture.

Contact: Any person exposed to a person with TB.

Contact investigation: Systematic identification of people, including children and adolescents, with previously undiagnosed TB disease and TB infection among the contacts of an index TB patient in the household and in comparable settings in which transmission occurs. It consists of identification, clinical evaluation and/or testing and provision of appropriate TB treatment (for people with confirmed TB) or TB preventive treatment (for people without TB disease).

Decentralization: Depending on the standard in the research settings used for the comparator, this includes provision of, access to or capacity for child and adolescent TB services at a lower level of

the health system than the lowest level where this is currently routinely provided. In most settings, decentralization applies to the district hospital (first referral level hospital) level and/or primary health care level and/or community level. Interventions for decentralization include capacity-building of various cadres of health care workers, expanding access to diagnostic services, ensuring availability of TB medicines for children and adolescents, and follow-up of children and adolescents with TB or on TB preventive treatment.

Differentiated HIV service delivery model: Person-centred approach to simplify provision of HIV services across the cascade in ways that better serve the needs of people living with HIV and reduce unnecessary burdens on the health system.

Drug susceptibility testing (DST): In vitro testing using either molecular genotypic techniques to detect resistance-conferring mutations, or phenotypic methods to determine susceptibility to a medicine.[2]

Extensive (or advanced) pulmonary tuberculosis disease: Presence of bilateral cavitary disease or extensive parenchymal damage on chest radiography (CXR). In children aged under 15 years, advanced disease is usually defined by the presence of cavities or bilateral disease on CXR.

Extensively drug-resistant tuberculosis (XDR-TB):[3]

- Pre-XDR-TB: TB caused by *Mycobacterium tuberculosis* strains that fulfil the definition of multidrug-resistant TB (MDR-TB) or rifampicin-resistant TB (RR-TB) and that are also resistant to any fluoroquinolone.[4]
- XDR-TB: TB caused by *M. tuberculosis* strains that fulfil the definition of MDR/RR-TB and that are also resistant to any fluoroquinolone and at least one additional Group A medicine.[5]

Extrapulmonary tuberculosis (EPTB) (classification): Any bacteriologically confirmed or clinically diagnosed case of TB involving organs other than the lungs (e.g. pleura, peripheral lymph nodes, abdomen, genitourinary tract, skin, joints and bones, meninges).[6]

Family-centred, integrated care: Family-centred models of care refer to interventions selected on the basis of the needs, values and preferences of the child or adolescent and their family or caregiver. This can include health education, communication, material or psychological support. Integrated services refer to approaches to strengthen collaboration, coordination, integration and harmonization of child and adolescent TB services with other child health-related programmes and services. This can include integration of models of care for TB screening, prevention, diagnosis and treatment with other existing service delivery platforms for maternal and child health (e.g. antenatal care, integrated community case management, integrated management of childhood illnesses) and other related services (e.g. HIV, nutrition, immunization). Other examples include evaluation of children and adolescents with common comorbidities (e.g. meningitis, malnutrition, pneumonia, chronic lung disease, diabetes, HIV) for TB and community health strategies integrating child and adolescent TB awareness, education, screening, prevention and case-finding into training and service delivery activities.

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2 Implementing tuberculosis diagnostics: a policy framework. Geneva: World Health Organization; 2015 (https://apps.who.int/iris/handle/10665/162712, accessed 11 March 2022).

3 Meeting report of the WHO expert consultation on the definition of extensively drug-resistant tuberculosis, 27–29 October 2020. Geneva: World Health Organization; 2021 (https://www.who.int/publications/i/item/meeting-report-of-the-who-expert-consultation-on-the-definition-of-extensively-drug-resistant-tuberculosis, accessed 11 March 2022).

4 The fluoroquinolones include levofloxacin and moxifloxacin as currently recommended by WHO for inclusion in shorter and longer regimens.

5 Group A medicines are currently levofloxacin or moxifloxacin, bedaquiline and linezolid; therefore, XDR-TB is MDR/RR-TB that is resistant to a fluoroquinolone and either bedaquiline or linezolid (or both). Group A medicines could change in the future. Therefore, the terminology "Group A" is appropriate here and will apply to any Group A medicines in the future.

6 Following a WHO expert consultation in September 2021, intrathoracic lymph node TB is now classified as pulmonary TB in children.

Grading of Recommendations Assessment, Development and Evaluation (GRADE): System for rating quality of evidence and strength of recommendations. This approach is explicit, comprehensive, transparent and pragmatic.[7]

High tuberculosis transmission setting: Setting with a high frequency of people with undetected or undiagnosed TB disease, or where people with infectious TB are present and there is a high risk of TB transmission. People with TB are most infectious when they are untreated or inadequately treated. Spread is increased by aerosol-generating procedures and by the presence of highly susceptible people.

Household contact: Person who shared the same enclosed living space as the index case for one or more nights or for frequent or extended daytime periods during the 3 months before the start of current treatment.

Index case (index patient) of tuberculosis: Initially identified person of any age with new or recurrent TB in a specific household or other comparable setting in which others may have been exposed. An index case is the person on which a contact investigation is centred but is not necessarily the source case.

Inpatient health care setting: Health care facility where people are admitted and assigned a bed while undergoing diagnosis and receiving treatment and care, for at least one overnight stay.

Integrated treatment decision algorithm: Flowchart allocating evidence-based scores to microbiological, clinical and radiological features that allow clinicians to make decisions regarding starting TB treatment in children.

Interferon-gamma release assay (IGRA): Blood test used to test for *Mycobacterium tuberculosis* infection by measuring the body's immune response to TB bacteria.

Multidrug-resistant tuberculosis (MDR-TB): TB caused by *Mycobacterium tuberculosis* strains that are resistant to at least both rifampicin and isoniazid.

New case: Newly registered episode of TB in a person who has never been treated for TB or has taken TB medicines for less than 1 month.

Non-severe pulmonary tuberculosis for the purpose of determining treatment duration for drug-susceptible tuberculosis: Intrathoracic lymph node TB without airway obstruction; uncomplicated TB pleural effusion or paucibacillary, non-cavitary disease confined to one lobe of the lungs and without a miliary pattern.

Number needed to screen: Number of people who need to undergo screening in order to diagnose one person with TB disease.

Operational research or implementation research: In the context of this document, applied research that aims to develop the critical evidence base that informs the effective, sustained and embedded adoption of interventions within a health system to improve health or patient outcomes. Such research deals with the knowledge gap between efficacy, effectiveness and current practice to produce the greatest gains in disease control.[8] Operational research also provides decision-makers with information to enable them to improve the performance of their health programmes.[9]

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[7] GRADE is a transparent framework for developing and presenting summaries of evidence. It provides a systematic approach for making clinical and public health practice recommendations. Guyatt GH, Oxman AD, Vist GE, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. BMJ. 2008;336:924.

[8] Guide to operational research in programs supported by the Global Fund. Geneva: Global Fund to Fight AIDS, Tuberculosis and Malaria; 2007 (https://www.who.int/hiv/pub/operational/or_guide_gf.pdf, accessed 11 March 2022).

[9] Expanding capacity for operations research in reproductive health: summary report of a consultative meeting. Geneva: World Health Organization; 2003 (https://apps.who.int/iris/bitstream/handle/10665/67936/WHO_RHR_02.18.pdf?sequence=1&isAllowed=y, accessed 11 March 2022).

Outpatient health care setting: Health care facility where people are undergoing diagnosis and receiving treatment and care but are not admitted for overnight stays (e.g. ambulatory clinic, dispensary).

Passive case-finding: Patient-initiated pathway to TB diagnosis involving a person with TB disease who experiences symptoms that they recognize as serious; the person having access to and seeking care, and presenting spontaneously at an appropriate health facility; a health worker correctly assessing that the person fulfils the criteria for presumptive TB; and successful use of a diagnostic algorithm with sufficient sensitivity and specificity to diagnose TB.

People who use drugs: People who engage in the harmful or hazardous use of psychoactive substances that could impact negatively on their health, social life, resources or legal situation.

Presumptive tuberculosis: Person who presents with symptoms or signs suggestive of TB.

Previously treated: People who have previously received 1 month or more of TB medicines. Previously treated people may have been treated with a first-line regimen for drug-susceptible TB or a second-line regimen for drug-resistant forms.

Programmatic management of tuberculosis preventive treatment: All coordinated activities by public and private health caregivers and the community aimed at scaling up TB preventive treatment to people who need it.

Pulmonary tuberculosis (PTB) (classification): Any bacteriologically confirmed or clinically diagnosed case of TB involving the lung parenchyma or the tracheobronchial tree, including tuberculous intrathoracic lymphadenopathy (mediastinal and/or hilar), without radiographic abnormalities in the lungs.[10] Miliary TB is classified as PTB because there are lesions in the lungs. A person with both PTB and extrapulmonary TB should be classified as having PTB.

Rifampicin-resistant tuberculosis (RR-TB): TB caused by *Mycobacterium tuberculosis* strains resistant to rifampicin. These strains may be susceptible or resistant to isoniazid (i.e. MDR-TB) or resistant to other first-line or second-line TB medicines. In these guidelines and elsewhere, MDR-TB and RR-TB cases are often grouped together as MDR/RR-TB and are eligible for treatment with an MDR-TB regimen.

Rifampicin-susceptible, isoniazid-resistant tuberculosis: TB caused by *Mycobacterium tuberculosis* strains resistant to isoniazid and susceptible to rifampicin.

Serious adverse event: Adverse event that can lead to death or a life-threatening experience, to hospitalization or prolongation of hospitalization, to persistent or significant disability, or to a congenital anomaly. Serious adverse events that do not immediately result in one of these outcomes but that require an intervention to prevent such an outcome from happening are included. Serious adverse events may require a drastic intervention, such as termination of the medicine suspected of having caused the event.

Severe acute malnutrition: Presence of oedema of both feet or severe wasting (weight-for-height/length less than −3 standard deviations/Z-scores or mid-upper arm circumference less than 115 mm).[11]

Severe extrapulmonary tuberculosis: Presence of miliary (disseminated) TB or TB meningitis. In children and young adolescents aged under 15 years, extrapulmonary forms of disease other than lymphadenopathy (peripheral nodes or isolated mediastinal mass without compression) are considered to be severe.

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[10] Following a WHO expert consultation in September 2021, intrathoracic lymph node TB is now classified as pulmonary TB in children.

[11] Pocket book of hospital care for children: guidelines for the management of common childhood illnesses, 2nd edition. Geneva: World Health Organization; 2013 (https://apps.who.int/iris/bitstream/handle/10665/81170/9789241548373_eng.pdf, accessed 27 September 2021).

Severe pneumonia: Cough or difficulty in breathing plus at least one of the following:

- central cyanosis or oxygen saturation <90% on pulse oximetry;
- severe respiratory distress (e.g. grunting, nasal flaring, very severe chest indrawing);
- signs of pneumonia with a general danger sign (inability to breastfeed or drink, persistent vomiting, lethargy or unconscious, convulsions, stridor in a calm child, severe malnutrition).[8]

Source case: Person with TB disease who infected others in a new setting. This could be the index patient or another person who was not identified.

Systematic screening for tuberculosis disease: Systematic identification of people at risk for TB disease in a predetermined target group by assessing symptoms and using tests, examinations or other procedures that can be applied rapidly. For those who screen positive, the diagnosis needs to be established by one or several diagnostic tests and additional clinical assessments. This term is sometimes used interchangeably with "active tuberculosis case-finding". It should be distinguished from testing for TB infection (with a TB skin test or interferon-gamma release assay).

Treatment outcomes and relapse: Categories for treatment outcomes used in this document and the term "relapse" were applied according to the definitions agreed for use by TB programmes, unless otherwise specified.[12,13]

Tuberculin skin test (TST): Intradermal injection of a combination of mycobacterial antigens that elicit an immune response (delayed-type hypersensitivity), represented by induration, which can be measured in millimetres. TST is used to diagnose TB infection.

Tuberculosis (TB): Disease state due to *Mycobacterium tuberculosis*. In this document, it is commonly referred to as "TB disease" to distinguish it from "TB infection".

Tuberculosis infection: State of persistent immune response to stimulation by *Mycobacterium tuberculosis* antigens with no evidence of clinically manifest TB disease. This is referred to as "TB infection" as distinct from "TB disease". There is no gold standard test for direct identification of *M. tuberculosis* infection in humans. Most infected people have no signs or symptoms of TB but are at risk for TB disease. The term "latent TB infection" has been replaced by the term "TB infection".

Tuberculosis preventive treatment (TPT): Treatment offered to people considered at risk of TB disease to reduce that risk. Also referred to as "treatment of TB infection" or "TB preventive therapy".

Underweight: Among adolescents, this usually refers to a body mass index below 18.5. Among children aged under 10 years, it usually refers to a weight-for-age Z-score below −2 standard deviations.

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[12] Definitions and reporting framework for tuberculosis – 2013 revision. Geneva: World Health Organization; 2013 (WHO/ HTM/TB/2013.2; http://apps.who.int/iris/bitstream/10665/79199/1/9789241505345_eng.pdf, accessed 11 March 2022).

[13] Meeting report of the WHO expert consultation on drug-resistant tuberculosis treatment outcome definitions, 17–19 November 2020. Geneva: World Health Organization; 2021 (https://apps.who.int/iris/rest/bitstreams/1336957/retrieve, accessed 11 March 2022).

Executive summary

Introduction

Children and young adolescents (aged below 15 years) represent about 11% of all people with tuberculosis (TB) globally. This means that 1.1 million children become ill with TB every year, almost half of them below five years of age. National TB programmes (NTPs) only notify less than half of these children, meaning that there is a large case detection gap *(1)*. The reasons for this gap include challenges with specimen collection and bacteriological confirmation of TB in young children, due to the paucibacillary nature of TB disease in this age group and the lack of highly sensitive point-of-care tests. In 2020, the COVID-19 pandemic had an additional negative impact on TB notifications in children. In addition to the case detection gap, only one third of child contacts below five years of age eligible for TB preventive treatment (TPT) received it in 2020. Young children are at higher risk of developing TB disease, including severe forms of TB, after TB infection, and the majority do so within a few months following exposure and infection *(2, 3)*. In addition to children and young adolescents, over half a million older adolescents (aged 15–19 years) are estimated to develop TB every year *(4)*.

The United Nations Sustainable Development Goal (SDGs) *(5)* and the World Health Organization (WHO) *End TB Strategy (6)* include targets to reduce TB incidence by 80% and TB deaths by 90% to be achieved by the year 2030, relative to baseline levels in 2015. In addition, to accelerate progress towards these global targets, the Resolution adopted by the United Nations General Assembly at the High-Level Meeting on the fight against tuberculosis in September 2018 commits to diagnosing and treating 40 million people with TB (including 3.5 million children), and 1.5 million people with drug-resistant TB (DR-TB) (including 115 000 children) by 2022. It also commits to providing at least 30 million people (including 4 million child contacts under five years of age), 20 million other household contacts (including children aged five years and above) and 6 million people living with HIV (including children) with TPT by 2022 *(7)*.

Rationale

To support countries in preventing and managing TB in children and adolescents, WHO's Global Tuberculosis Programme published the WHO *Guidance for national tuberculosis programmes on the management of tuberculosis in children (second edition)* in 2014 *(8)*. Since the publication of the second edition, new evidence related to diagnostic approaches for TB, treatment for drug-susceptible TB, DR-TB and TB meningitis, as well as models of care relevant to children and adolescents has become available. The *WHO consolidated guidelines on tuberculosis. Module 5: management of tuberculosis in children and adolescents* (2022) is a consolidated guideline of new and existing recommendations (see annex 1), and replaces the 2014 guidance. It complements existing WHO guidelines on the management of TB, recognizing the unique characteristics and needs of these groups, as well as those of their parents, caregivers and families. The guidelines are complemented by the *WHO operational handbook on tuberculosis. Module 5: Management of tuberculosis in children and adolescents*, which provides guidance on how to implement the recommendations in the guidelines.

Objectives

The objectives of the 2022 consolidated guidelines are: to provide policy-makers and implementing partners with evidence-based recommendations on the cascade of care for children and adolescents; to support the implementation of activities to prevent TB among children and adolescents at risk; to improve TB case detection and treatment outcomes in children and adolescents with TB using effective models of care; and to contribute to reductions in TB related morbidity and mortality in children and adolescents in line with global targets including those in the SDGs *(5)*, the WHO End TB Strategy *(6)* and the Political declaration of the UN General Assembly High-Level Meeting on the fight against tuberculosis *(7)*.

Target audience

The target audience for these consolidated guidelines consists primarily of NTPs, primary health care (PHC) programmes, maternal and child health programmes, national AIDS programmes (or their equivalents in health ministries) and other health policy-makers. They also target generalist and specialist paediatricians, clinicians and health practitioners working on TB, HIV and/or infectious diseases in public and private sectors, the educational sector, nongovernmental, civil society and community-based organizations, as well as technical and implementing partners.

Recommendations on the management of TB in children and adolescents

A WHO convened Guideline Development Group (GDG) meeting held in 2021 led to eight new recommendations on the management of TB in children and adolescents (Table 1). A summary of the recommendations consolidated in this guideline are listed in Table 2 below.

A summary of all new and consolidated recommendations can be found in web annex 5.

Table 1: New recommendations in the *WHO consolidated guidelines on tuberculosis. Module 5: management of tuberculosis in children and adolescents, 2022*

Diagnostic approaches
1   In children with signs and symptoms of pulmonary TB, Xpert Ultra should be used as the initial diagnostic test for TB and detection of rifampicin resistance on sputum, nasopharyngeal aspirate, gastric aspirate or stool, rather than smear microscopy/culture and phenotypic drug susceptibility testing (DST).   *(**UPDATED**: strong recommendation, moderate certainty of evidence for test accuracy in stool and gastric aspirate; low certainty of evidence for test accuracy in sputum; very low certainty of evidence for test accuracy in nasopharyngeal aspirate)*
2   In children with presumptive pulmonary TB attending health care facilities, integrated treatment decision algorithms may be used to diagnose pulmonary TB.   *(**NEW**: interim, conditional recommendation, very low certainty of evidence)*
Treatment regimens
3   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.   *(**NEW**: strong recommendation, moderate certainty of evidence)*

4	In children with MDR/RR-TB aged below 6 years, an all-oral treatment regimen containing bedaquiline may be used. (***NEW****: conditional recommendation, very low certainty of evidence*)[14]	

5	In children with MDR/RR-TB aged below 3 years delamanid may be used as part of longer regimens. (***NEW****: conditional recommendation, very low certainty of evidence*)[15]

6	In children and adolescents with bacteriologically confirmed or clinically diagnosed TB meningitis (without suspicion or evidence of MDR/RR-TB), a 6-month intensive regimen (6HRZEto) may be used as an alternative option to the 12-month regimen (2HRZE/10HR). (***NEW****: conditional recommendation, very low certainty of evidence*)

Models of TB care

7	In high TB burden settings, decentralized TB services may be used in children and adolescents with signs and symptoms of TB and/or in those exposed to TB. (***NEW****: conditional recommendation, very low certainty of evidence*)

8	Family-centred, integrated services in addition to standard TB services may be used in children and adolescents with signs and symptoms of TB and/or those exposed to TB. (***NEW****: conditional recommendation, very low certainty of evidence*)

Table 2: Recommendations in the *WHO consolidated guidelines on tuberculosis. Module 5: management of tuberculosis in children and adolescents,* 2022, by chapter and topic

Chapter	Topic
Screening and contact investigation	Screening for TB in targeted populations
	Tools for screening for TB
	HIV counselling and testing for household and close contacts of people with TB
Prevention	TB infection prevention and control: administrative controls
	TB infection prevention and control: environmental controls
	TB infection prevention and control: respiratory protection
	BCG vaccination: BCG vaccination at birth vs at six weeks
	BCG vaccination: Selective BCG vaccination
	BCG vaccination: Need for revaccination
	BCG vaccination: BCG vaccination for HIV-infected infants

[14] This recommendation applies to and complements the 2020 WHO recommendations on shorter and longer regimens that contain bedaquiline: A shorter all-oral bedaquiline-containing regimen of 9–12 months duration is recommended in eligible patients with confirmed multidrug- or rifampicin-resistant tuberculosis (MDR/RR-TB) who have not been exposed to treatment with second-line TB medicines used in this regimen for more than one month, and in whom resistance to fluoroquinolones has been excluded *(Conditional recommendation, very low certainty in the evidence);* bedaquiline should be included in longer multidrug-resistant TB (MDR-TB) regimens for patients aged 18 years or more *(Strong recommendation, moderate certainty in the estimates of effect);* bedaquiline may also be included in longer MDR-TB regimens for patients aged 6–17 years; *(Conditional recommendation, very low certainty in the estimates of effect) (9).*

[15] This recommendation complements the 2020 WHO recommendation on longer regimens that contain delamanid: Delamanid may be included in the treatment of MDR/RR-TB patients aged 3 years or more on longer regimens *(Conditional recommendation, moderate certainty in the estimates of effect) (9).*

	TB preventive treatment: Identifying populations for TB infection testing and TB preventive treatment – People living with HIV
	TB preventive treatment: Identifying populations for TB infection testing and TB preventive treatment – Household contacts (regardless of HIV status)
	TB preventive treatment: Identifying populations for TB infection testing and TB preventive treatment – Other people at risk
	TB preventive treatment: Algorithms to rule out TB disease
	TB preventive treatment: Testing for TB infection
	TB preventive treatment: TB preventive treatment options
Diagnostic approaches	Use of commercial serodiagnostics
	Xpert MTB/RIF and Xpert Ultra as initial tests in adults and children with signs and symptoms of pulmonary TB
	Xpert MTB/RIF and Xpert Ultra as initial tests in adolescents and children with signs and symptoms of extrapulmonary TB
	Xpert MTB/RIF and Xpert Ultra repeated testing in children and adolescents with signs and symptoms of pulmonary TB
	Xpert MTB/RIF and Xpert Ultra as initial tests for pulmonary TB in adults in the general population either with signs and symptoms of TB or chest radiography with lung abnormalities or both
	Truenat MTB, MTB Plus and Truenat MTB-RIF Dx in adults and children with signs and symptoms of pulmonary TB
	Moderate complexity automated nucleic acid amplification tests (NAATs) for detection of TB and resistance to rifampicin and isoniazid
	Loop-mediated isothermal amplification
	Lateral flow urine lipoarabinomannan (LF-LAM) assay
	Low complexity NAATs for detection of resistance to isoniazid and second-line TB agents
	First-line line-probe assay (LPAs)
	Second-line line-probe assays (SL-LPAs)
	High complexity reverse hybridization-based NAATs for detection of pyrazinamide resistance

Treatment	Treatment of severe forms of pulmonary TB in children	
	Treatment of infants aged 0–3 months with TB	
	Treatment of osteoarticular TB in children	
	Use of thrice weekly dosing and fixed dose combination tablets	
	Use of corticosteroids in TB meningitis	
	A 4-month treatment regimen composed of isoniazid, rifapentine, moxifloxacin and pyrazinamide for treatment of drug-susceptible pulmonary TB	
	Regimen for rifampicin-susceptible and isoniazid-resistant TB	
	Shorter all-oral bedaquiline-containing regimen for multidrug- or rifampicin-resistant TB (MDR/RR-TB)	
	Longer regimens for MDR/RR-TB	
	The bedaquiline, pretomanid and linezolid (BPaL) regimen for MDR-TB with additional fluoroquinolone resistance	
	Monitoring patient response to MDR-TB treatment using culture	
Models of TB care	Health education and counselling	
	Treatment adherence interventions	
	Treatment administration options	
	Ambulatory care for persons with MDR-TB	
	Decentralized model of care for persons with MDR-TB	
Special situations	Routine HIV testing for persons with presumptive and diagnosed TB	
	Co-trimoxazole prophylaxis for infants, children and adolescents living with HIV	
	General recommendations on eligibility for ART	
	Timing of ART for children and adolescents with TB	
	First-line ART regimens	
	Second-line ART regimens	
	Management of severe acute malnutrition (SAM)	
	Management of moderate undernutrition	
	Contact investigation	

Based on these guidelines, tools to support implementation have been developed, including new integrated treatment decision algorithms and an updated table on dosing of second-line TB medicines. In accordance with the process for updating WHO guidelines, a systematic and continuous process of identifying and bridging evidence gaps following guideline dissemination will be employed. If new evidence that could potentially impact the current evidence base for any of the recommendations is identified, it will be reviewed with a view to updating the recommendation. WHO welcomes suggestions regarding additional questions for inclusion in future updates of the guideline.[16]

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[16] The WHO Global Tuberculosis Programme can be contacted at gtbprogramme@who.int.

Main changes to the 2014 guidance in the 2022 update

The 2014 WHO *Guidance for national tuberculosis programmes on the management of tuberculosis in children (second edition) (8)* included 28 recommendations on the management of TB in children. The 2022 consolidated guidelines incorporate: recommendations from the 2014 guidelines that remain valid (mainly topics that remain key components of high-quality TB care for which no new evidence was assessed), relevant recommendations that have since been published in other WHO guidelines, and new recommendations published in 2022. A summary of the changes to the 2014 guidance is provided in the supplementary table in annex 2. Also, the focus of the 2022 consolidated guidelines is on children and adolescents aged 0–19 years, whereas the previous guidelines focused on children and to a lesser extent, younger adolescents (aged 10–14 years).

1. Introduction

1.1. Background

Children and young adolescents (aged below 15 years) represent about 11% of all people with TB globally. This means that close to 1.1 million children become ill with TB every year, almost half of them below five years of age. National TB programmes (NTPs) only notify less than half of these children, meaning that there is a large case detection gap *(1)*. The reasons for this gap include challenges with specimen collection and bacteriological confirmation of TB in young children, due to the paucibacillary nature of TB disease in this age group and the lack of highly sensitive point-of-care tests *(10)*. In 2020, the COVID-19 pandemic had an additional negative impact on TB notifications in children, with a 24% decrease in notifications compared to 2019 (in comparison, notifications in people aged 15 years and above decreased by 18%). In addition to the case detection gap, only one third of child contacts below five years of age eligible for TB preventive treatment (TPT) actually received it in 2020 *(1)*. Young children are at higher risk of developing TB disease, including severe forms of TB, than older age groups, after TB infection, and the majority do so within a few months following exposure and infection *(2, 3)*. In addition to children and young adolescents, over half a million older adolescents (15–19 years) are estimated to develop TB every year *(4)*.

The United Nations Sustainable Development Goal (SDGs) *(5)* and the World Health Organization (WHO) *End TB Strategy (6)* include targets to reduce TB incidence by 80% and TB deaths by 90% to be achieved by the year 2030, relative to baseline levels in 2015. In addition, the Resolution adopted by the United Nations General Assembly (UNGA) at the High-Level Meeting on the fight against tuberculosis in September 2018 commits to diagnosing and treating 40 million people with TB (including 3.5 million children), and 1.5 million people with DR-TB (including 115 000 children) by 2022. It also commits to providing at least 30 million people (including 4 million child contacts under five years of age), 20 million other household contacts (including children over the age of five years) and 6 million people living with HIV (including children) with TPT by 2022 *(7)*.

To support countries in preventing and managing TB in children and adolescents, WHO's Global Tuberculosis Programme published the *WHO Guidance for national tuberculosis programmes on the management of tuberculosis in children (second edition)* in 2014. Since these guidelines were published, new recommendations and guidance on the management of TB have been published in WHO guidelines and other policy documents on TB prevention, screening, diagnosis, treatment, management and models of care. Many of these recommendations are also applicable to children and adolescents. In addition, new evidence related to the management of TB in children and adolescents became available to WHO in 2021. Some of these data were received in response to a specific request from WHO for data on the management of TB in children and adolescents, issued as an Expression of Interest in July 2020,[17] which was developed in consultation with the core team of the Child and Adolescent TB Working group.[18] Data from a randomized controlled trial on treatment shortening for children with non-severe TB were made available to the WHO in 2021. Therefore, in 2021, the WHO convened a Guideline Development Group (GDG) to review new evidence on the management of TB in children and adolescents. This guideline update includes new recommendations that were

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[17] WHO public call for data on the management of TB in children and adolescents. 24 July 2020. WHO [website] (https://www.who.int/news-room/articles-detail/who-public-call-for-data-on-the-management-of-tb-in-children-and-adolescents, accessed 20 January 2022).

[18] Child and Adolescent TB Working Group (https://www.stoptb.org/wg/dots_expansion/childhoodtb/, accessed 20 January 2022).

issued at the GDG meeting in May-June 2021 as well as current recommendations from other WHO guidelines that are relevant to the management of TB in children and adolescents (including those that are in the previous guidelines on the management of TB in children that have been validated). This update consolidates all recommendations in one guideline.

1.2. Rationale for the development of the 2022 consolidated guidelines

Since the publication of the WHO *Guidance for national tuberculosis programmes on the management of tuberculosis in children (second edition*) (2014) *(8)*, there have been numerous studies, including reviews, randomized controlled trials, observational studies, pharmacokinetic (PK) and pharmacodynamic studies, qualitative research and cost-effectiveness research, which have evaluated the impact of various interventions. These are related to diagnostic approaches for TB, treatment for drug-susceptible TB (DS-TB), drug-resistant TB (DR-TB) and TB meningitis (TBM), as well as models of TB care, relevant to children and adolescents. Therefore, it was timely to review this new evidence and to update the recommendations from 2014. Other recommendations in the 2014 guidance were reviewed for their continued relevance. It was agreed that the new guidelines should be consolidated, bringing together new recommendations as well as existing recommendations with relevance to children and adolescents.

1.3. Objectives of the 2022 consolidated guidelines

The objectives of the 2022 consolidated guidelines on the management of TB in children and adolescents are to:

1. provide policy-makers and implementing partners with evidence-based recommendations on the entire cascade of care for children and adolescents to support the implementation of activities to prevent TB among children and adolescents at risk, and to improve TB case detection and treatment outcomes in children and adolescents with TB, using effective models of care; and

2. contribute to reductions in TB-related morbidity and mortality in children and adolescents in line with global targets including those in the SDGs *(5)*, the End TB Strategy *(6)* and the Political declaration of the UN General Assembly High-Level Meeting on the fight against tuberculosis *(7)*.

1.4. Target audience

The target audience for these consolidated guidelines consists primarily of NTPs, primary health care (PHC) programmes, maternal and child health programmes, national AIDS programmes (or their equivalents in health ministries) and other health policy-makers. They also target generalist and specialist paediatricians, clinicians and health practitioners working on TB, HIV and/or infectious diseases in public and private sectors, the educational sector, nongovernmental, civil society and community-based organizations, as well as technical and implementing partners.

1.5. WHO recommendations relevant to the management of TB in children and adolescents

The 2022 consolidated guidelines represent a significant update compared to the previous guidelines issued in 2014. They include: (i) new recommendations based on the review of newly available evidence related to the Population, Intervention, Comparator and Outcomes (PICO) questions that were developed for this guideline update; (ii) recommendations with relevance to children and adolescents from other WHO TB guidelines issued since 2014; and (iii) a few recommendations from

the 2014 guidance that remain unchanged. These latter recommendations cover key components of high-quality TB care for which a review of the evidence was either not done (such as HIV testing for persons with presumptive TB and TB disease), or for which no new evidence was available. A summary of the changes to the 2014 guidance is provided in the supplementary table in annex 2.

The full details of the new recommendations, including evidence and justification, subgroup and implementation considerations and monitoring and evaluation, are provided in this guideline. Other WHO recommendations relevant to the management of TB in children and adolescents have been consolidated in tables in the relevant chapters. It is important to note that the original wording of the recommendations based on the source guidelines has been included. In some source guidelines, age groups have been defined differently compared to the 2022 consolidated guidelines on the management of TB in children and adolescents, and the adult age group may include adolescents aged 15 years and above. Where this is the case, it has been indicated in the tables. Users of this guideline update are advised to refer to the original guideline for full information related to the recommendation. In addition, all WHO recommendations on TB are now included in the WHO TB Knowledge Sharing Platform (KSP)[19] which can be searched by population (e.g. children or people living with HIV) or by topic (e.g. diagnosis or treatment). Refer to section 1.7 for further details.

For ease of reference, a full overview of all new and consolidated recommendations is included in web annex 5.

1.6. Scope of the guideline update

The population of interest in these guidelines is children and adolescents, defined as:

- A child is a person under 10 years of age.
- An adolescent is a person 10–19 years of age (inclusive).

The pathway of TB infection and disease in an individual child or adolescent, and the interface with and retention across sequential stages of care (termed the 'cascade of care') was used as the analytic framework during the scoping process for this guideline update (Figure 1) *(10)*. This pathway involves multiple steps from exposure to a person with an infectious form of TB, leading to subsequent TB infection and, for some, progression to TB disease. Each of the steps in the cascade of care requires evidence-based interventions to reduce TB transmission, prevent TB, enable early and accurate diagnosis of TB and optimize treatment outcomes for children with drug-susceptible or DR-TB. In addition, child-, adolescent- and family-friendly services are needed to optimize access to high quality care.

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[19]   WHO TB Knowledge Sharing Platform (https://extranet.who.int/tbknowledge)

Figure 1: Cascade of care in children and adolescents exposed to and with TB, with broad topics of PICO questions with corresponding numbers as per section 1.3.1
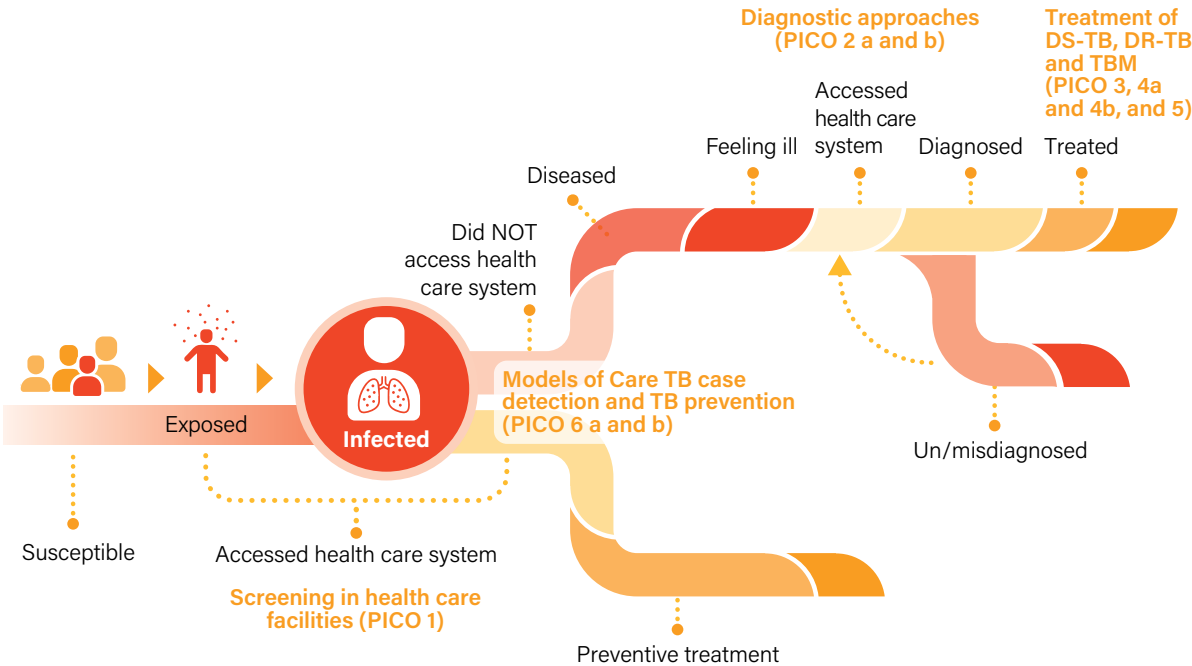
Source: Roadmap towards ending TB in children and adolescents. Second edition. Geneva: World Health Organization; 2018.

DS/DR-TB: drug-susceptible/drug-resistant TB; TBM: TB meningitis.

Based on this understanding of the cascade of TB care in children and adolescents, the potential contribution of interventions targeting different steps in this cascade is summarized in the following logic model (which was the model used to frame these guidelines) with the potential contribution of the evidence to short-term and long-term outcomes (Figure 2).

Figure 2: The logic model used for the guidelines on the management of TB in children and adolescents

Inputs	Activities	Short-term outcomes*	Long-term outcomes*
• Stakeholder engagement from all sectors in the community • Financial resources • Human resources • Equipment and supplies • Participation by families with children and adolescents exposed to or with (presumptive) TB • Community participation • Infection control at community level • Evidence from research	• Contact investigation • TB screening activities • Diagnostic approaches for relevant forms of DS- and DR-TB • Optimal treatment regimens for the treatment of DS- and DR-TB • Innovative models of care to deliver TB services to children and adolescents • Capacity building of health care workers at all levels • Demand generation at community level	• Earlier and increased detection of DS- and DR-TB in children and adolescents *(1, 2, 6)* • Improved TB treatment outcomes *(3, 4, 5)* • Increase in TB preventive treatment coverage in children and adolescents *(6)* • Improved quality of child and adolescent TB care *(6)*	• Reduced TB incidence and prevalence in children and adolescents *(1, 2, 6)* • Reduced TB mortality in children and adolescents *(1, 3, 4, 5, 6)* • Reduced post-TB sequelae in children and adolescents *(4, 5)* • Reduced financial losses due to TB, for families and for the community *(1, 2, 3, 6)*

*The numbers under short- and long-term outcomes refer to the PICO questions in section 1.6.1.

DS/DR-TB: drug-susceptible/drug-resistant TB.

A WHO Steering Group drafted a series of PICO (questions, which were discussed and agreed upon by the GDG during a preparatory webinar. Systematic reviews or other studies were sought or commissioned for each of the PICO questions. In addition, two priority background questions were formulated to provide additional insight into implementation considerations related to TB care for children and adolescents. After a review of preliminary data, the GDG recommended that one PICO question (PICO question 1 on TB screening) should not be further pursued as the evidence for this question overlapped directly with the evidence reviewed for the *WHO consolidated guidelines on tuberculosis. Module 2: screening – systematic screening for tuberculosis disease*, published in 2021 *(11)*. Therefore, this PICO question was not considered by the GDG at their meeting in May-June 2021.

1.6.1. PICO questions

PICO question 1: TB screening approaches in children <10 years of age

Which screening tools should be used to screen systematically for TB disease in children aged below 10 years accessing health care?

a. In children aged below 10 years accessing health care in high TB prevalence settings, should systematic screening for PTB using chest radiography (CXR) be used against a composite reference standard?
b. In children aged below 10 years accessing health care in high TB prevalence settings, should systematic screening for pulmonary TB using symptom screen be used against a composite reference standard?

PICO question 2: TB diagnostic approaches in children

a. In children aged below 10 years with presumptive pulmonary TB attending health care facilities, should integrated treatment-decision algorithms be used to diagnose pulmonary TB, compared to a microbiological or composite reference standard?
b. In children aged below 10 years with signs and symptoms of pulmonary TB, seeking care at health care facilities, should Xpert Ultra in gastric aspirate or stool be used to diagnose pulmonary TB and rifampicin resistance, as compared with a microbiological/composite reference standard?
    i.   What is the diagnostic accuracy of Xpert Ultra in gastric aspirate and stool for pulmonary TB in children aged below 10 years, as compared with a microbiological and composite reference standard?
    ii. What is the diagnostic accuracy of Xpert Ultra in gastric aspirate and stool for rifampicin resistance in children aged below 10 years, as compared with a microbiological and composite reference standard?

PICO question 3: Treatment shortening in children and adolescents with non-severe drug-susceptible TB

In children and adolescents with non-severe TB, should a 4-month intervention regimen versus the standard 6-month regimen conforming to WHO guidelines be used?

PICO question 4: Treatment of rifampicin-resistant/multidrug resistant TB (MDR/RR-TB)

a. In MDR/RR-TB patients aged below 6 years, should an all-oral treatment regimen containing bedaquiline versus other regimens conforming to WHO guidelines without bedaquiline be used?
b. In MDR/RR-TB patients aged below 3 years, should an all-oral treatment regimen containing delamanid versus other regimens conforming to WHO guidelines without delamanid be used?

PICO question 5: Treatment of paediatric TB meningitis

In children and adolescents with presumed or bacteriologically confirmed drug-susceptible TB meningitis, should a 6-month intensive regimen, compared to the 12-month regimen that conforms to current WHO guidelines be used?

PICO question 6: Models of care for TB case detection and TB prevention settings with a prevalence of TB in the general population of 100 per 100 000 or more:

a. In children and adolescents with signs and symptoms of TB, should decentralization of child and adolescent TB services versus centralized child and adolescent TB services (at referral or tertiary hospital level) be used?

b. In children and adolescents exposed to TB, should decentralization of child and adolescent TB prevention and care services versus centralized prevention and care services (at referral or tertiary hospital level) be used to increase coverage of TPT in eligible children and adolescents?

c. In children and adolescents with signs and symptoms of TB, should family-centred, integrated services versus standard, non-family-centred, non-integrated services be used?

d. In children and adolescents exposed to TB, should family-centred, integrated services versus standard, non-family-centred, non-integrated services be used to increase coverage of TPT in eligible children and adolescents?

1.6.2. Background questions

a. What is the socioeconomic impact of TB on children and adolescents and their families?

b. How can adolescents with TB or eligible for TPT be optimally engaged in their care?

1.7. Publication, dissemination, evaluation and expiry

The electronic version of the consolidated guidelines on the management of TB in children and adolescents will form part of the WHO TB KSP, which features the following components for each TB module: (i) consolidated guidelines, (ii) operational handbooks with implementation guidance; as well as (iii) a catalogue of WHO e-learning materials.

Further dissemination strategies include global, regional and country webinars and consultations, development of training materials based on the guideline and the operational handbook, and technical support for countries during programme reviews and other in-country missions, as well as review of national strategic plans and funding applications.

Data collected for the annual global TB reports will be evaluated to monitor TB notification rates for children (0–4 and 5–9 years) and adolescents (10–14 and 15–19 years), the proportion of notified TB cases that are children and young adolescents under 15 years (for both DS-TB and DR-TB, and TB treatment coverage rates for children under 5 years, children and young adolescents 5–14 years of age. Other indicators that will be monitored include TB treatment outcomes for children and young adolescents under the age of 15 years as well as coverage of TPT among eligible contacts under the age of 5 years, as well as older contacts.

The recommendations included in the 2022 consolidated guidelines will be considered for updating in five years' time, or earlier if new evidence becomes available. For the interim recommendation on the use of treatment decision algorithms, new data will be generated and reviewed within a two-year time period.

1.8. Document structure

A summary of the structure of the guidelines including a brief description of the contents is provided in Box 1.

Box 1: Structure of the 2022 consolidated guidelines

→ **Chapter 1** is the introduction and provides background information, an overview of the scope (including PICO and background questions), the rationale, objectives and target audience for the guidelines.

→ **Chapter 2** includes WHO recommendations on TB screening and contact investigation that are relevant to children and adolescents. While no new recommendations were made in these areas by the GDG on the management of TB in children and adolescents, new recommendations on TB screening in children and adolescents were issued by WHO in 2021. These include recommendations on the populations to be screened (persons living with HIV infection and close contacts) and the screening tools that can be applied. The other recommendations in this chapter relate to contact investigation.

→ **Chapter 3** focuses on TB prevention. It includes existing recommendations on TB infection prevention and control as well as TPT. The recommendations on TPT relate to the identification of populations who should be tested for TB infection, algorithms to rule out TB disease, tests for TB infection and TPT regimens. This chapter also includes recommendations on BCG vaccination that were published in a WHO position paper in 2018.

→ **Chapter 4** includes WHO recommendations on diagnostic approaches. Two new recommendations were made in the 2021 GDG meeting on: (i) the use of Xpert Ultra in gastric aspirate and stool specimens to diagnose pulmonary TB and rifampicin resistance; and (ii) the use of integrated treatment decision algorithms in children with presumptive pulmonary TB. Other recommendations in this chapter include existing WHO recommendations on rapid diagnostic tests including Xpert MTB/RIF, Xpert Ultra, Truenat MTB, MTB Plus and Truenat MTB-RIF Dx, lateral flow urine lipoarabinomannan (LF-LAM) assays, low complexity automated nucleic acid amplification tests, line probe assays and high complexity reverse hybridization-based nucleic acid amplification tests.

→ **Chapter 5** focuses on TB treatment. Four new recommendations were made by the child and adolescent TB GDG on TB treatment: (i) a 4-month regimen for children and adolescents 3 months to 16 years of age with non-severe drug-susceptible TB; (ii) a 6-month intensive regimen to treat TB meningitis composed of isoniazid, rifampicin, pyrazinamide and ethionamide; (iii) use of bedaquiline as part of shorter or longer regimens for children of all ages to treat MDR/RR-TB; and (iv) use of delamanid as part of longer regimens for children of all ages to treat MDR/RR-TB. A summary of other valid treatment recommendations is also consolidated in this chapter, including for drug susceptible and DR-TB and for severe forms of EPTB.

→ **Chapter 6** includes WHO recommendations on models of care. Two new recommendations on models of care arose in 2021 including one on decentralized care and another on integrated family-centred care. Other WHO recommendations in this chapter include existing recommendations on health education and counselling, treatment adherence interventions, treatment support and decentralized care for people with MDR/RR-TB.

→ **Chapter 7** includes existing WHO recommendations on several specific situations such as care of the child or adolescent living with TB and HIV, care of children with TB and malnutrition, and optimal feeding of infants born to mothers with TB. The recommendations on HIV include those on HIV testing, eligibility for and timing of antiretroviral therapy (ART), co-trimoxazole prophylaxis and treatment regimens for ART.

→ **Chapter 8** describes research priorities that were identified at the GDG meeting in 2021. These signal areas where additional evidence is needed to improve the prevention, management and care of TB in children and adolescents.

2. TB screening and contact investigation

This chapter includes current WHO recommendations that apply to children and adolescents on TB screening and contact investigation. They have been consolidated from current WHO guidelines on systematic screening for TB disease and contact investigation, namely the *WHO consolidated guidelines on tuberculosis. Module 2: screening – systematic screening for tuberculosis disease (11)* and *Guidance for national tuberculosis programmes on the management of tuberculosis in children (second edition) (8)*. For more information on each recommendation including the remarks, source of evidence, justification, subgroup, implementation and monitoring and evaluation considerations, the source guidelines or WHO TB KSP should be consulted.

Table 3: WHO recommendations on TB screening and contact investigation relevant to children and adolescents

WHO consolidated guidelines on tuberculosis. Module 2: screening – systematic screening for tuberculosis disease *(11)*
Screening for TB in targeted populations
Household contacts and other close contacts of individuals with TB disease should be systematically screened for TB disease.   *(Strong recommendation, moderate certainty of evidence)*
People living with HIV should be systematically screened for TB disease at each visit to a health facility.   *(Strong recommendation, very low certainty of evidence)*
Systematic screening for TB disease may be conducted among subpopulations with structural risk factors for TB. These include urban poor communities, homeless communities, communities in remote or isolated areas, indigenous populations, migrants, refugees, internally displaced persons and other vulnerable or marginalized groups with limited access to health care.   (*Existing recommendation: conditional recommendation, very low certainty of evidence*).
Tools for screening for TB
Among individuals aged 15 years and older in populations in which TB screening is recommended, systematic screening for TB disease may be conducted using a symptom screen, chest X-ray or molecular WHO-recommended rapid diagnostic tests, alone or in combination.   *(Conditional recommendation, very low certainty of evidence for test accuracy)*

Among individuals aged 15 years and older in populations in which TB screening is recommended, computer-aided detection software programmes may be used in place of human readers for interpreting digital chest X-rays for screening and triage for TB disease.

(Conditional recommendation, low certainty of evidence)

Among adults and adolescents living with HIV, systematic screening for TB disease should be conducted using the WHO-recommended four symptom screen and those who report any one of the symptoms of current cough, fever, weight loss or night sweats may have TB and should be evaluated for TB and other diseases.

(Strong recommendation, moderate certainty of evidence)

Among adults and adolescents living with HIV, C-reactive protein using a cut-off of >5 mg/L may be used to screen for TB disease.

(Conditional recommendation, low certainty of evidence for test accuracy)

Among adults and adolescents living with HIV, chest X-ray may be used to screen for TB disease.

(Conditional recommendation, moderate certainty of evidence for test accuracy)

Among adults and adolescents living with HIV, molecular WHO-recommended rapid diagnostic tests may be used to screen for TB disease.

(Conditional recommendation, moderate certainty of evidence for test accuracy)

Adult and adolescent inpatients with HIV in medical wards where the TB prevalence is >10% should be tested systematically for TB disease with a molecular WHO-recommended rapid diagnostic test.

(Strong recommendation, moderate certainty of evidence for test accuracy)

Among individuals younger than 15 years who are close contacts of someone with TB, systematic screening for TB disease should be conducted using a symptom screen including any one of cough, fever or poor weight gain; or chest radiography; or both.

(Strong recommendation, moderate to low certainty of evidence for test accuracy)

Among children younger than 10 years who are living with HIV, systematic screening for TB disease should be conducted using a symptom screen including any one of current cough, fever, poor weight gain or close contact with a TB patient.

(Strong recommendation, low certainty of evidence for test accuracy)

Guidance for national tuberculosis programmes on the management of tuberculosis in children. Second edition *(8)*

In settings of high HIV prevalence, all household and close contacts of people with TB should be counselled and tested for HIV.

(Strong recommendation, very low certainty of evidence)

In settings of low HIV prevalence, all household members and close contacts of people with TB who have symptoms compatible with TB disease may be offered counselling and testing for HIV as part of their clinical evaluation.

(Conditional recommendation, very low certainty of evidence)

All household contacts of an index case who is a person living with HIV should be counselled and tested for HIV.

(Strong recommendation, very low certainty of evidence)

3. Prevention of TB

This chapter includes current WHO recommendations that apply to children and adolescents on TB prevention. They have been consolidated from current WHO guidelines on TB infection, prevention and control, a BCG position paper and guidelines on TPT, namely the *WHO guidelines on tuberculosis infection prevention and control, 2019 update (12)*, the *BCG vaccines: WHO position paper* (published in the Weekly Epidemiological Record) *(13)* and the *WHO consolidated guidelines on tuberculosis. Module 1: prevention – tuberculosis preventive treatment (14)*. For more information on each recommendation including the remarks, source of evidence, justification, subgroup, implementation and monitoring and evaluation considerations, the source guidelines or WHO TB KSP should be consulted.

Table 4: WHO recommendations on TB infection prevention and control, BCG vaccination and TPT relevant to children and adolescents

TB infection prevention and control: WHO guidelines on tuberculosis infection prevention and control, 2019 update *(12)*
Administrative controls
Triage of people with TB signs and symptoms, or with TB disease, is recommended to reduce *M. tuberculosis* transmission to health workers (including community health workers (CHW)), persons attending health care facilities or other persons in settings with a high risk of transmission. *(Conditional recommendation, very low certainty in the estimates of effects)*
Respiratory separation/isolation of people with presumed or demonstrated infectious TB is recommended to reduce *M. tuberculosis* transmission to health workers or other persons attending health care facilities. *(Conditional recommendation, very low certainty in the estimates of effects)*
Prompt initiation of effective TB treatment of people with TB disease is recommended to reduce *M. tuberculosis* transmission to health workers, persons attending health care facilities or other persons in settings with a high risk of transmission. *(Strong recommendation, very low certainty in the estimates of effects)*
Respiratory hygiene (including cough etiquette) in people with presumed or confirmed TB is recommended to reduce *M. tuberculosis* transmission to health workers, persons attending health care facilities or other persons in settings with a high risk of transmission. *(Strong recommendation, low certainty in the estimates of effects)*
Environmental controls
Upper-room germicidal ultraviolet (GUV) systems are recommended to reduce *M. tuberculosis* transmission to health workers, persons attending health care facilities or other persons in settings with a high risk of transmission. *(Conditional recommendation, moderate certainty in the estimates of effects)*

Ventilation systems (including natural, mixed-mode, mechanical ventilation and recirculated air through high-efficiency particulate air (HEPA) filters) are recommended to reduce *M. tuberculosis* transmission to health workers, persons attending health care facilities or other persons in settings with a high risk of transmission.

(Conditional recommendation, very low certainty in the estimates of effects)

Respiratory protection

Particulate respirators, within the framework of a respiratory protection programme, are recommended to reduce *M. tuberculosis* transmission to health workers, persons attending health care facilities or other persons in settings with a high risk of transmission.

(Conditional recommendation, very low certainty in the estimates of effects)

BCG vaccination: BCG vaccines: WHO position paper, 2018 *(13)*

Bacillus Calmette-Guérin (BCG) vaccination at birth vs at 6 weeks

In countries or settings with a high incidence of TB and/or leprosy, a single dose of BCG vaccine should be given to neonates at birth, or as soon as possible thereafter, for prevention of TB and leprosy disease. If it cannot be given at birth, it should be given at the earliest opportunity thereafter and should not be delayed. Any delay in vaccination may lead to opportunities for known or unknown exposure to TB or leprosy-infected contacts.

Co-administration of BCG with the hepatitis B birth dose is safe and strongly recommended. In order to avoid missed opportunities for neonatal vaccination, BCG multi-dose vials should be opened and used despite any wastage of unused vaccine.

If the birth dose was missed, catch-up vaccination of unvaccinated older infants and children is recommended since evidence shows it is beneficial. Catch-up vaccination should be done at the earliest convenient encounter with the health care system to minimize known or unknown exposure to TB or leprosy infected contacts.

Selective BCG vaccination

Countries with a low incidence of TB or leprosy may choose to selectively vaccinate neonates in recognized risk groups for developing disease. High-risk groups to be considered for BCG vaccination include the following:

• Neonates to parents (or other close contacts/relatives) with previous TB or leprosy

• Neonates in households with contacts to countries with high incidence of TB and/or leprosy

• Neonates in any other locally identified risk group for TB and/or leprosy

In a few countries with low TB incidence, BCG vaccination is largely replaced by intensified case detection, contact tracing and supervised early treatment.

Need for revaccination

Studies show minimal or no evidence of any additional benefit of repeat BCG vaccination against TB or leprosy. Therefore, revaccination is not recommended even if the TST reaction or result of an IGRA is negative. The absence of a BCG scar after vaccination is not indicative of a lack of protection and is not an indication for revaccination.

BCG vaccination for HIV-infected infants

Children who are HIV-infected when vaccinated with BCG at birth are at increased risk of developing disseminated BCG disease. However, if HIV-infected individuals including children, are receiving ART, are clinically well and immunologically stable (CD4% >25% for children aged <5 years or CD4 count ≥200 if aged >5 years) they should be vaccinated with BCG.

• In general, populations with high prevalence of HIV infection also have the greatest burden of TB; in such populations the benefits of potentially preventing severe TB through vaccination at birth are outweighed by the risks associated with the use of BCG vaccine. Therefore, it is recommended that in such populations:

  – Neonates born to women of unknown HIV status should be vaccinated as the benefits of BCG vaccination outweigh the risks.

  – Neonates of unknown HIV status born to HIV-infected women should be vaccinated if they have no clinical evidence suggestive of HIV infection, regardless of whether the mother is receiving ART.

  – Although evidence is limited, for neonates with HIV infection confirmed by early virological testing, BCG vaccination should be delayed until ART has been started and the infant confirmed to be clinically and immunologically stable (CD4% >25%).

TB preventive treatment: WHO consolidated guidelines on tuberculosis. Module 1 – prevention – tuberculosis preventive treatment, 2020 *(14)*

Identifying populations for TB infection testing and TPT – people living with HIV

Adults and adolescents living with HIV who are unlikely to have TB disease should receive TB preventive treatment as part of a comprehensive package of HIV care. Treatment should also be given to those on antiretroviral treatment, to pregnant women and to those who have previously been treated for TB, irrespective of the degree of immunosuppression and even if TB infection testing is unavailable.

(Strong recommendation, high certainty in the estimates of effect)

Infants aged <12 months living with HIV who are in contact with a person with TB and who are unlikely to have TB disease on an appropriate clinical evaluation or according to national guidelines should receive TB preventive treatment.

(Strong recommendation, moderate certainty in the estimates of effect)

Children aged ≥12 months living with HIV who are considered unlikely to have TB disease on an appropriate clinical evaluation or according to national guidelines should be offered TB preventive treatment as part of a comprehensive package of HIV prevention and care if they live in a setting with high TB transmission, regardless of contact with TB.

(Strong recommendation, low certainty in the estimates of effect)

All children living with HIV who have successfully completed treatment for TB disease may receive TB preventive treatment.

(Conditional recommendation, low certainty in the estimates of effect)

Identifying populations for TB infection testing and TB preventive treatment – household contacts (regardless of HIV status)

Children aged <5 years who are household contacts of people with bacteriologically confirmed pulmonary TB and who are found not to have TB disease on an appropriate clinical evaluation or according to national guidelines should be given TB preventive treatment even if TB infection testing is unavailable.

(Strong recommendation, high certainty in the estimates of effect)

Children aged ≥5 years adolescents and adults who are household contacts of people with bacteriologically confirmed pulmonary TB who are found not to have TB disease by an appropriate clinical evaluation or according to national guidelines may be given TB preventive treatment.

(Conditional recommendation, low certainty in the estimates of effect)

In selected high-risk household contacts of patients with multidrug-resistant tuberculosis, preventive treatment may be considered based on individualized risk assessment and a sound clinical justification.

(Conditional recommendation, very low certainty in the estimates of effect)

Identifying populations for TB infection testing and TB preventive treatment – other people at risk

(these populations may include children and adolescents)

People who are initiating anti-TNF[20] treatment, or receiving dialysis, or preparing for an organ or haematological transplant, or who have silicosis should be systematically tested and treated for TB infection.

(Strong recommendation, low to very low certainty in the estimates of effect)

Systematic TB infection testing and treatment may be considered for prisoners, health workers, immigrants from countries with a high TB burden, homeless people and people who use drugs.

(Conditional recommendation, low to very low certainty in the estimates of effect)

Systematic TB infection testing and treatment is not recommended for people with diabetes, people who engage in the harmful use of alcohol, tobacco smokers and underweight people unless they also belong to other risk groups included in the above recommendations.

(Conditional recommendation, very low certainty in the estimates of effect)

Algorithms to rule out TB disease

Adults and adolescents living with HIV should be screened for TB according to a clinical algorithm. Those who do not report any of the symptoms of current cough, fever, weight loss or night sweats are unlikely to have TB disease and should be offered preventive treatment, regardless of their antiretroviral treatment (ART) status.

(Strong recommendation, moderate certainty in the estimates of effect)

Adults and adolescents living with HIV who are screened for TB according to a clinical algorithm and who report any of the symptoms of current cough, fever, weight loss or night sweats may have TB disease and should be evaluated for TB and other diseases and offered preventive treatment if TB disease is excluded.

(Strong recommendation, moderate certainty in the estimates of effect)

Chest radiography may be offered to people living with HIV on ART and preventive treatment given to those with no abnormal radiographic findings.

(Conditional recommendation, low certainty in the estimates of effect)

Infants and children living with HIV who have poor weight gain, fever or current cough or who have a history of contact with a person with TB should be evaluated for TB and other diseases that cause such symptoms. If TB disease is excluded after an appropriate clinical evaluation or according to national guidelines, these children should be offered TB preventive treatment, regardless of their age.

(Strong recommendation, low certainty in the estimates of effect)

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[20] TNF: tumour necrosis factor

The absence of any symptoms of TB and the absence of abnormal chest radiographic findings may be used to rule out TB disease among HIV-negative household contacts aged ≥5 years and other risk groups before preventive treatment.

(Conditional recommendation, very low certainty in the estimates of effect)

Testing for TB infection

Either a tuberculin skin test (TST) or interferon-gamma release assay (IGRA) can be used to test for TB infection.

(Strong recommendation, very low certainty in the estimates of effect)

TB preventive treatment options

The following options are recommended for the treatment of TB infection regardless of HIV status: 6 or 9 months of daily isoniazid, or a 3-month regimen of weekly rifapentine plus isoniazid,[21] or a 3-month regimen of daily isoniazid plus rifampicin.

(strong recommendation, moderate to high certainty in the estimates of effect).

A 1-month regimen of daily rifapentine plus isoniazid[22] or 4 months of daily rifampicin alone may also be offered as alternatives.

(Conditional recommendation, low to moderate certainty in the estimates of effect)

In settings with high TB transmission, adults and adolescents living with HIV who have an unknown or a positive TB infection test, and are unlikely to have TB disease, should receive at least 36 months of daily isoniazid preventive therapy (IPT). Daily IPT for 36 months should be given whether or not the person is on ART, and irrespective of the degree of immunosuppression, history of previous TB treatment and pregnancy in settings considered to have a high TB transmission as defined by national authorities.

(Conditional recommendation, low certainty in the estimates of effect)

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[21] In children 2 years and above.

[22] In children 13 years and above.

4. Diagnostic approaches for TB in children and adolescents

Of the estimated 1.1 million children who developed TB annually, only 399 000 (36.5%) were notified to NTPs in 2020. Under-notification is worst among children below 5 years of age, with only 27.5% of children with TB being notified *(1)*. These 'missing' children are not diagnosed and/or not reported. TB-related mortality among children below 15 years of age was estimated at 226 000 for 2020 *(1)*. Modelling has shown that 80% of TB-related deaths are among children under 5 years of age, and that 96% of children who die of TB, did not access treatment *(15)*.

The low case detection rate among (young) children is due to several factors including: the fact that young children have paucibacillary TB and do not excrete enough bacilli to be detectable by available bacteriological tests; the lack of a sensitive point-of-care diagnostic test; difficulties in collecting suitable respiratory samples for bacteriological confirmation; and misdiagnosis due to the overlap of non-specific symptoms of TB with other common childhood diseases. Children often first access care at the PHC level, where there may be little or no awareness and capacity to diagnose and manage children with TB (this includes capacity for sample collection, access to bacteriological tests and CXR, as well as capacity and confidence in making a clinical diagnosis when bacteriological testing is not available or is negative). In addition, paediatric TB services are often highly centralized at secondary or tertiary levels of the health system and managed in a vertical, non-integrated way. TB screening is often not systematically incorporated into clinical algorithms for child health *(10)*.

This chapter contains two new recommendations relevant to the diagnosis of TB in children and adolescents as well as other valid WHO recommendations that apply to children and adolescents on TB diagnosis. The two new recommendations relate to the use of the Xpert Ultra assay in gastric aspirate and stool specimens for the diagnosis of PTB and detection of rifampicin resistance among children, and the use of integrated treatment decision algorithms[23] for the diagnosis of PTB in children. Prior to 2022, Xpert Ultra had already been recommended for use in nasopharyngeal aspirate (NPA) and sputum specimens; hence, the 2022 recommendation widens the number of specimens that can be used and aligns this with the WHO recommendation on Xpert MTB/RIF (which WHO recommends for use in gastric aspirate, NPA, sputum and stool specimens to diagnose PTB and detect rifampicin resistance) *(16)*. The two new recommendations are described in detail in this chapter.

Section 4.3 consolidates recommendations from current WHO guidelines on rapid diagnostic tests and the use of commercial serodiagnostic tests, namely the *WHO consolidated guidelines on tuberculosis. Module 3: diagnosis – rapid diagnostics for tuberculosis detection, 2021 update (16)* and the *Commercial serodiagnostic tests for diagnosis of tuberculosis: policy statement (17)*. For more information on each recommendation including the remarks, source of evidence, justification, subgroup, implementation and monitoring and evaluation considerations, the source guidelines or WHO's TB KSP should be consulted.

The WHO convened an expert consultation on the classification of intrathoracic TB disease among children in September 2021. The experts reviewed evidence from the point of view of pathophysiology,

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[23]   Treatment decision algorithms are defined as: A flow chart allocating evidence-based scores to microbiological, clinical and radiological features that allow clinicians to make a decision regarding starting TB treatment in children.

clinical and surveillance, and advised the WHO to update the classification of intrathoracic TB lymphadenopathy in children as PTB.

4.1. The use of the Xpert MTB/RIF Ultra assay in gastric aspirate and stool specimens for the diagnosis of pulmonary TB and rifampicin resistance

Recommendation:

In children with signs and symptoms of pulmonary TB, Xpert Ultra should be used as the initial diagnostic test for TB and detection of rifampicin resistance on sputum, nasopharyngeal aspirate, gastric aspirate or stool, rather than smear microscopy/culture and phenotypic drug susceptibility testing (DST).

(*Strong recommendation, moderate certainty of evidence for test accuracy in stool and gastric aspirate; low certainty of evidence for test accuracy in sputum; very low certainty of evidence for test accuracy in nasopharyngeal aspirate*).

Remarks

- The recommendation on the use of Xpert Ultra to detect rifampicin resistance in stool and gastric aspirate was extrapolated from existing recommendations on its use in other sample types.
- Considerations regarding the acceptability and feasibility of implementation of both stool and gastric aspirate specimens need to be taken into account.

4.1.1. Justification and evidence

The development of the Xpert MTB/RIF assay (Cepheid, Sunnyvale, United States of America (United States)) was a significant step forward in improving the diagnosis of TB and the detection of rifampicin resistance globally. However, Xpert MTB/RIF sensitivity is suboptimal, particularly among people (including children) with smear-negative TB and people (including children) living with HIV. The Xpert MTB/RIF Ultra (Cepheid, Sunnyvale, United States), hereafter referred to as Xpert Ultra, was developed by Cepheid as the next-generation assay to overcome these limitations. Xpert Ultra has a lower limit of detection than the Xpert MTB/RIF, with an additional "trace" semi-quantitative category. It uses the same GeneXpert® platform as the Xpert MTB/RIF. Xpert MTB/RIF is strongly recommended as the initial diagnostic test for TB and rifampicin-resistance detection in sputum (including induced and spontaneously expectorated sputum), gastric aspirate, NPA and stool specimens rather than smear microscopy/culture and phenotypic DST in children aged below 15 years with signs and symptoms of PTB. The Xpert Ultra assay is recommended in the same population as the initial diagnostic test for TB and detection of rifampicin resistance in sputum or NPA, rather than smear microscopy/culture and phenotypic DST *(16)*.

The 2020 rapid diagnostics guidelines and 2021 update listed the evaluation of the diagnostic accuracy of Xpert Ultra in gastric aspirate or stool specimens for PTB in children as a research priority. Therefore, a systematic review and meta-analysis were conducted to evaluate the use of the Xpert Ultra assay in two paediatric specimens, namely gastric aspirate and stool, for which insufficient data were available at the time of the GDG meeting on molecular assays in December 2019 *(18)*.

PICO question: In children aged below 10 years of age with signs and symptoms of pulmonary TB seeking care at health care facilities, should Xpert Ultra in gastric aspirate or stool be used to diagnose pulmonary TB and rifampicin resistance, as compared with a microbiological/composite reference standard?

Evidence: In preparation for the GDG meeting on the management of TB in children and adolescents, an update of the review on the diagnostic accuracy of Xpert MTB/RIF and Xpert Ultra for TB disease in children *(18)* was performed. A systematic search of the literature was carried out in January 2021. This update focused specifically on the diagnostic accuracy of Xpert Ultra in gastric aspirate or lavage specimens and stool specimens for the diagnosis of PTB and rifampicin resistance in children below 10 years of age. Nine studies that evaluated the diagnostic accuracy of Xpert Ultra in gastric aspirate and/or stool specimens in children were identified. For the meta-analysis, six studies (653 participants) provided data for gastric specimens *(19–24)* and six studies (1278 participants) for stool specimens *(20, 23–27)*. The review found that for gastric aspirate, Xpert Ultra sensitivity was 64% in children 0–9 years, against a microbiological reference standard and specificity was 95%. For stool, Xpert Ultra sensitivity was 53% in children 0–9 years, against the microbiological reference standard and specificity was 98%. Sensitivity estimates against a composite reference standard were lower for both specimen types. There were no studies that evaluated the diagnostic accuracy of Xpert Ultra for detection of rifampicin resistance using gastric aspirate or stool specimens.

Of the nine studies, eight (89%) reported the proportion of Xpert Ultra positive results that were trace results. In these eight studies, of the total Xpert Ultra positive results, the proportion (expressed as a percentage) of Ultra trace results ranged from 0% to 66% (median 52%) in studies evaluating gastric specimens and from 0% to 84% (median 52%) in studies evaluating stool specimens.

GDG considerations: The GDG members discussed that all TB tests, including the microbiological reference standard (usually culture or Xpert Ultra on respiratory samples) have suboptimal sensitivity in children, due to the paucibacillary nature of TB disease in this age group. Therefore, the panel highlighted that a positive test accurately determines a case of TB disease, but a negative test does not exclude TB disease. As no studies assessed the diagnostic accuracy for Xpert Ultra for the detection of rifampicin resistance in children, conclusions related to the use of Xpert Ultra for the diagnosis of rifampicin resistance were based on data in adults, evaluated for the 2020 rapid diagnostic guidelines. The GDG members agreed that the desirable effects from the test in both specimens are moderate, but large for the detection of rifampicin resistance, because of the large impact on the choice of effective treatment when rifampicin resistance is detected. The panel noted that false-negative results should be interpreted within the context of the clinical picture, and clinicians should not solely use a negative test to rule out disease. The GDG judged that the balance of effects favours the intervention (considering both the moderate desirable effects and small undesirable effects), based on moderate certainty evidence for both gastric aspirate and stool samples.

The GDG judged that more time and training-related resources would be required to collect gastric aspirate specimens, and that the procedure would also often require hospital admission. Stool processing may result in some additional time requirement to prepare the sample, depending on the processing method. The panel decided upon comparing the cost of doing the tests on the sample types versus not doing the test. The panel then concluded that the costs for both specimen types vary.

While there were no studies on the cost-effectiveness of gastric aspirate, a cost-effectiveness study compared stool testing against clinical diagnosis at PHCs in Uganda, assuming that no respiratory samples would be collected without referral to the hospital or without invasive sampling (see web annex 4). Compared to that standard of care, stool testing was more effective, but also more costly. The GDG members discussed that an Xpert Ultra test on stool samples becomes cost-effective even at a TB prevalence level of 3% at a zero discount rate (the practice of discounting future health effects). Implementation aspects such as the importance of obtaining microbiological confirmation and the detection of rifampicin resistance would further favour cost-effectiveness of stool testing. The panel therefore concluded that the evidence probably favours Xpert Ultra testing on stool samples.

In terms of acceptability, although the gastric aspirate sample collection was found to be an invasive procedure (that could be uncomfortable to children), the panel felt that the procedure is probably acceptable to children, caregivers and health care workers (HCW), considering the role of this procedure to obtain bacteriological confirmation at higher level facilities. The GDG noted the importance of

non-invasiveness of stool samples for bacteriological testing for the diagnosis of TB in children and agreed that this sample type was acceptable to all relevant stakeholders, including HCWs, laboratory technicians, parents and children.

The panel agreed that, despite the requirements of training and skills, using Xpert Ultra on gastric aspirate is probably feasible to implement, especially at higher levels of the health care system. The majority of the panel felt that Xpert Ultra on stool samples is feasible to implement at all levels of the health care system (see web annex 3).

4.1.2. Subgroup considerations

Children with severe acute malnutrition (SAM): four studies (with 259 participants, of whom 9 had TB disease) were identified for children with SAM using Xpert Ultra on gastric aspirates and three studies (428 participants, 19 with TB) using Xpert Ultra on stool specimens. The meta-analysis on stool samples in children with SAM showed similar accuracy as in the overall analysis (sensitivity 63.2%, specificity 98.5%). A meta-analysis on gastric aspirates could not be performed due to insufficient data.

Children living with HIV infection: four studies (99 participants, 8 with TB disease) were identified for children living with HIV using Xpert Ultra on gastric aspirates and two studies (100 participants, 3 with tuberculosis) using Xpert Ultra on stool specimens. A meta-analysis on stool or gastric aspirate samples could not be conducted for children living with HIV due to paucity of data.

Age subgroups: analyses on age subgroups were conducted by systematic reviewers.

- For **gastric aspirate** samples from ***children aged below 1 year***, Xpert Ultra pooled sensitivity and specificity (95% CI) were 67.3% (43.5 to 84.6) and 94.0% (84.7 to 97.8) respectively (5 studies, 182 participants; low-certainty (sensitivity) and moderate-certainty (specificity) evidence). From ***children aged 1 to 4 years***, Xpert Ultra pooled sensitivity and specificity (95% CI) were 71.5% (40.0 to 90.4) and 94.0% (73.8 to 98.9), respectively (4 studies, 327 participants; low-certainty evidence).
- For **stool** samples from ***children aged below 1 year***, Xpert Ultra pooled sensitivity and specificity (95% CI) were 65.2% (33.7 to 87.3) and 96.2% (88.9 to 98.7), respectively (4 studies, 295 participants; very low-certainty (sensitivity) and moderate-certainty (specificity) evidence). From ***children aged 1 to 4 years***, Xpert Ultra pooled sensitivity and specificity (95% CI) were 43.3% (27.1 to 61.2) and 97.1% (74.8 to 99.7), respectively (3 studies, 331 participants; very low-certainty (sensitivity) and low-certainty (specificity) evidence). The small number of children aged below 1 year and in the 1–4 years age group for both samples limited the confidence in the precision of the estimates for these age groups.

The systematic review did not identify studies that evaluated Xpert Ultra in gastric aspirate or stool samples of children with ***severe pneumonia***.

Xpert Ultra on gastric aspirate, stool, NPA and sputum (expectorated or induced) samples can be used in all paediatric comorbidity and age subgroups mentioned in this section as the preferred initial test for the diagnosis of PTB in children.

4.1.3. Implementation considerations

Specimen collection and the quality thereof needs to be ensured to optimize accurate diagnosis for all specimen types.

Gastric aspirate samples: Gastric aspirate sample collection in children requires trained staff and access to supplies. It may also require hospitalization and may therefore not be feasible at lower levels of the health system. It is considered an invasive procedure, requires fasting and may be uncomfortable and less acceptable to children and caregivers, or have adverse effects. Referral

systems need to be functional to ensure that children who need to be tested using gastric samples reach the appropriate level of care.

Stool samples: Stool sampling has the advantage of being non-invasive, with the collection generally perceived as easy and feasible by HCWs and caregivers, irrespective of the clinical condition of the child. The possible drawback is that children may not be able to pass stool on command causing delay in sample collection. Enhancing awareness and sensitizing caregivers on stool as a suitable sample for TB testing is important, to enhance acceptability and implementation. Stool processing is also an acceptable procedure for laboratory technicians and regarded as a good alternative to sputum samples. Relatively high rates of non-determinate Xpert Ultra results (including error, invalid, or no results) were reported in the studies included in the systematic review. These rates varied from less than 1% to 10% and may depend on the stool processing method used.

Stool processing methods: An analysis of preliminary results of a head-to-head comparison of three centrifuge-free stool processing methods combined with Xpert Ultra was conducted to inform implementation considerations on the use of Xpert Ultra in stool samples. The three processing methods were optimized sucrose flotation (OSF) *(28)*, simple one step stool (SOS) *(29)* and stool processing kit (SPK) *(25)*. The results at the time of the GDG meeting showed a similar performance of Xpert Ultra in combination with the three stool processing methods, in terms of sensitivity and specificity. All methods were found to be easy to process by laboratory staff at the reference laboratory level and had a high ease-of-use score. However, most users considered that these methods cannot be performed by non-laboratory personnel (such as nurses or HCWs) in PHC settings without access to a laboratory. Overall, the SOS method appeared to be the preferred method as it does not require additional equipment and is comparable to sputum processing using Xpert Ultra. The SPK is still at prototype stage but will not be commercialized; the optimized sucrose flotation is still under validation, and its development into a kit format to simplify some of the steps is envisaged in the near future. Therefore, either of the available centrifuge-free stool processing methods may be used, depending on local preference and laboratory infrastructure.

Xpert Ultra trace results: Trace results are common with the use of Xpert Ultra in all paediatric specimen types, reflecting the paucibacillary nature of TB disease in children. For children as well as people living with HIV who are being evaluated for PTB, and for persons being evaluated for EPTB, the "*M. tuberculosis* complex (MTBC) detected trace" Ultra result is considered as bacteriological confirmation of TB *(30)*. This is an important implementation consideration, in view of the risk of morbidity and mortality in these populations. Trace results will have an indeterminate result for rifampicin resistance; therefore, alternative specimens may need to be collected for Xpert Ultra processing in persons with a high likelihood of drug resistance.

4.1.4. Monitoring and evaluation

Local monitoring of specimen collection by specimen type, diagnostic test, result and clinical diagnosis in a TB Laboratory Register (or equivalent) is recommended. Results should be recorded in a TB Register.

Routine recording and reporting of child and adolescent notifications in five-year age brackets (i.e. 0–4, 5–9, 10–14, 15–19 years) is recommended by WHO for countries with case-based electronic recording and reporting systems.

4.2. Treatment decision algorithms for the diagnosis of pulmonary TB in children aged below 10 years of age

Interim recommendation

In children with presumptive pulmonary TB attending health care facilities, integrated treatment decision algorithms may be used to diagnose pulmonary TB.

(Conditional recommendation, very low certainty of evidence).

Remarks

- Presumptive TB refers to a person who presents with symptoms and/or signs suggestive of TB.[24]

- Bacteriological confirmation should be sought as part of the integrated treatment decision algorithms whenever possible, using WHO recommended rapid diagnostic tests and appropriate paediatric specimens (including stool, nasopharyngeal aspirate, induced or expectorated sputum or gastric aspirate).

- In follow-up to the GDG meeting, new integrated treatment decision algorithms for specific populations and settings, have been developed and internally validated. These algorithms are detailed with practical guidance on their use in the operational handbook on the management of tuberculosis in children and adolescents.[25] National TB and other health programmes are encouraged to use these evidence-based algorithms.

- This interim recommendation will remain valid for a period of 24 months after the publication of these guidelines, after which new evidence will be reviewed.

4.2.1. Justification and evidence

TB diagnosis in children relies on a thorough assessment of all evidence derived from a careful history of exposure, clinical examination and relevant investigations. While various algorithms and scoring systems for TB diagnosis in children exist, these have not been systematically evaluated. There is a need for evidence-based, practical treatment decision algorithm(s), ideally for different settings with varying access to diagnostic tests and CXR.

PICO question: In children aged below 10 years with presumptive pulmonary TB attending health care facilities, should integrated treatment-decision algorithms be used to diagnose pulmonary TB, compared to a microbiological or composite reference standard?

Evidence: To address the need for evaluating and developing evidence-based, integrated treatment decision algorithm(s), ideally for different settings with varying access to diagnostic tests and CXR, an individual participant dataset (IPD) meta-analysis was conducted. For this analysis, an IPD meta-cohort was developed, consisting of diagnostic evaluations data from children aged below 10 years, to infer the sensitivity and specificity of treatment-decision algorithms (or scores) in identifying pulmonary TB, using the updated clinical case definitions for the classification of intrathoracic TB among children *(31)*. Data were requested from investigators in February 2021. Data for the IPD was sourced from several studies carried out within a geographically diverse set of TB high-burden countries. Algorithm sensitivity and specificity in classifying TB was evaluated against the Union Desk Guide Algorithm *(32)*, which

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24   Definitions and reporting framework for tuberculosis – 2013 revision (updated December 2014 and January 2020). Geneva: World Health Organization; 2013.

25   WHO operational handbook on tuberculosis. Module 5: management of tuberculosis in children and adolescents (https://apps.who.int/iris/bitstream/handle/10665/352523/9789240046832-eng.pdf).

was developed in an attempt to operationalize the 2014 WHO guidance *(8)* by outlining the steps that a health care worker should take in evaluating a child with presumptive PTB.

To make full use of available data for comparing the performance of these algorithms in different settings, missing variables were imputed, heterogeneous definitions of variables were collapsed, and slight modifications were made to the algorithms or scores to enable the use of the variables available in the IPD. A total of 14 studies, comprising 5494 records were included, of which 4811 records were included in this analysis *(26, 33–47)*. Studies from 13 countries (including 12 high TB, TB/HIV and/or MDR-TB burden countries) within 5 of the 6 WHO regions were included. The cohort in the meta-analysis used to inform this recommendation had a median age of 26 months (interquartile range 13.4–58.3); 38% of the children had TB, of which 30% was bacteriologically confirmed; 20% of the children were living with HIV infection; and 14% had SAM.

Seven algorithms or scoring systems were identified for evaluation, comprising the Uganda National TB/Leprosy Control Program (NTLP) algorithm *(48)*, the Brazilian Ministry of Health Child PTB Scoring System *(49)*, the Gunasekera et al. 2021 algorithm *(50)*, the Keith Edward score *(51)*, the Marcy et al. 2019 algorithm *(52)*, the Stegen-Toledo score *(53)*, and the Marais et al. 2006 criteria *(54)*. The pooled estimates of the sensitivity and specificity of each algorithm/score were compared to the standard of care algorithm (i.e. The Union Desk Guide Algorithm, which constituted the reference standard *(32)*) for children aged below 10 years, for children living with HIV, for children with SAM and for children aged below 1 year.

For the overall population of children under the age of 10 years, the pooled sensitivity of the seven algorithms or scoring systems ranged from 16% (Marais et al. criteria) to 95% (Gunasekera et al. algorithm), while the pooled specificity ranged from 9% (Gunasekera et al. algorithm) to 89% (Marais et al. criteria) (see web annex 3).

GDG considerations: The GDG felt that algorithms with clinical criteria have an important role to play in making decisions on starting children on TB treatment, particularly at peripheral levels of the health care system. There was strong consensus among the GDG members about the need and importance of working on treatment decision algorithms to improve the gaps in TB case detection in children. An important advantage of evidence-based algorithms (as it allocates a modelled weight to features of clinical evaluation), is that this modelling process allows for specification of the weight of certain clinical features, rather than being based solely on expert opinion. The panel highlighted that data in the IPD were mainly from tertiary settings where the proportion of children with confirmed TB is higher than at district hospital or PHC level. It was acknowledged that the IPD had a high level of heterogeneity. Conducting a meta-regression analysis by level of the health care system was not possible because of the limited number of studies.

The GDG concluded that none of the evaluated algorithms were optimal in terms of either sensitivity or specificity, combined with the very low certainty of evidence. The GDG also noted that algorithms with a high sensitivity (i.e. low number of false negatives) generally have a low specificity (i.e. a high number of false positives) and vice versa. The panel reflected on the consequences of false negative and false positive conclusions based on integrated treatment decision algorithms and agreed that it was most important to avoid missing a TB diagnosis in a child who has TB, considering the large case detection gap and the consequences of a missed diagnosis of TB.

During the GDG deliberations, the following options that emerged from the evidence review were discussed: (i) choose one of the algorithms reviewed for a possible recommendation; (ii) make a generic recommendation on the use of integrated treatment decisions algorithms and present new evidence-based algorithms in the operational handbook; (iii) make a statement about the need for further research on treatment decision algorithms, affirming the need for such algorithms.

The GDG judged the available evidence as inappropriate to support a recommendation for any specific algorithm; and instead decided to make a generic recommendation on the use of treatment decision

algorithms, and to describe newly developed algorithms for relevant subgroups and/or settings in the operational handbook. The decision for a generic recommendation considers the current practice of HCWs making decisions on starting TB treatment in children based on a combination of clinical signs and symptoms, history of TB contact and investigations, and the need to develop evidence-based approaches for this practice. In addition, an interim conditional recommendation was deemed most appropriate, considering the need to reduce the TB case detection gap in children and the need for additional evidence on the use of integrated treatment decision algorithms in programmatic settings.

The GDG also prioritized the need to reduce false negative results, while accepting a certain degree of over-diagnosis, as well as limiting unnecessary referrals and tests for children. The GDG members judged that a general recommendation with operational guidance on the use of evidence-based algorithms integrating the use of rapid diagnostics with clinical features would empower HCWs, including those in settings with limited access to diagnostic tools, to make decisions on starting TB treatment in children.

The GDG concluded that a period of 24 months for the interim conditional recommendation would be needed to: set up and conduct studies to generate new data, including studies to externally validate the algorithms, implementation/operational research, modelling studies to determine the potential impact of the treatment decision algorithms and qualitative research into feasibility and acceptability for health care workers and families (refer to chapter 8 on detailed research priorities).

4.2.2. Subgroup considerations

For **HIV-infected children under the age of 10 years,** the pooled sensitivity of the algorithms reviewed ranged from 24% (Marais et al. criteria) to 92% (Uganda NTLP algorithm), and the pooled specificity from 15% (Uganda NTLP algorithm) to 87% (Stegen-Toledo score, cut-off 5).

For **children with SAM** the pooled sensitivity varied between 33% (Marais et al. criteria) and 93% (Uganda NTLP algorithm and Keith Edward score), while the pooled specificity varied between 10% (Keith Edward score) and 88% (Stegen-Toledo score, cut-off 5).

For **infants aged below 1 year** the pooled sensitivity ranged from 17% (Marais et al. criteria) to 93% Gunasekera et al. algorithm) and the pooled specificity from 13% (Gunasekera et al. algorithm) to 86% (Stegen-Toledo score, cut-off 5).

The GDG members highlighted the need for the development of specific evidence-based treatment decision algorithms for specific subgroups at high risk of rapid progression of TB disease, including children living with HIV, children with SAM and infants, if possible.

4.2.3. Implementation considerations

Algorithms included in the operational handbook: In the follow-up to the GDG meeting, new integrated treatment decision algorithms for specific populations and settings have been developed and internally validated, using regression modelling with pre-determined cut-off values for sensitivity and specificity against the reference standard (using updated clinical case definitions to define pulmonary TB, outlined in Graham S et al. *(31)*), based on the individual patient data set used for the evidence review conducted to answer this PICO question. The algorithms are described in the operational handbook and cover the diagnosis of PTB among children under the age of 10 years, including intrathoracic lymphadenopathy. The algorithms are not suitable for the diagnosis of EPTB.

Implementation at peripheral levels of the health system: Integrated treatment decision algorithms allow treatment decisions to be made at more decentralized levels of care, where children generally present earlier, with less severe disease and lower bacteriological confirmation rates. Algorithms integrating clinical criteria have an important role to play at these levels of the health system.

The decision to start treatment is linked to other recommendations in these guidelines, such as shortening of the treatment duration for children with non-severe forms of TB and on decentralization of TB services. Once a decision to start TB treatment has been made, the severity of disease needs to be assessed to inform the duration of treatment. Detailed criteria for assessing severity of disease are described in the operational handbook.

Referral: Defining the criteria for referral of children evaluated for PTB at peripheral levels of the health care system using the algorithms is important. Examples of subgroups in need of referral include infants, children with presumptive severe forms of EPTB (such as TBM, disseminated TB and osteoarticular TB) and children with presumptive DR-TB in regions with a high prevalence of DR-TB. Children presenting with severe acute pneumonia need referral to the appropriate level of care for oxygen supplementation, while children with SAM need to be provided with appropriate nutritional support. A high index of suspicion is important among infants with acute symptoms who are contacts of people with bacteriologically confirmed TB, to make a treatment decision as soon as possible rather than wait for symptoms to persist. This is due to the potential for rapid deterioration in the clinical condition of infants and development of severe TB disease.

Clinical monitoring of children started on TB treatment: It is important to acknowledge that the preference for sufficient sensitivity of the algorithms to detect and treat children with TB will mean that some children who do not have TB will be treated with TB treatment. The risk of severe drug-related toxicity in children is very low, and shorter regimens for non-severe TB (see chapter 5) will further reduce the risks related to treatment. However, it will be critical to monitor children started on TB treatment and to refer them for evaluation for other diseases and appropriate treatment if they fail to respond to TB treatment within 1 month.

Implementation in high DR-TB burden settings: Integrated treatment decision algorithms may be implemented in settings with a high burden of DR-TB. Seeking bacteriological confirmation using appropriate paediatric samples and WHO recommended rapid diagnostic tests (such as Xpert MTB/RIF or Ultra) is critical among children who have a history of contact with a source case with confirmed or highly likely DR-TB (including a TB patient not responding to treatment, or a source case who died of TB while on treatment). Once a decision to treat a child without bacteriological confirmation for TB has been made based on the algorithm, risk factors for the child having DR-TB need to be assessed. Clinicians need to keep a high index of suspicion for DR-TB in these children and ensure they are tested and managed for DR-TB as appropriate (see chapter 5).

4.2.4. Monitoring and evaluation

The integrated treatment decision algorithms need to be monitored and evaluated for their impact on case notifications and treatment outcomes.

Clinical monitoring of people with TB started on treatment based on clinical criteria is equally important, such as the need to monitor response to treatment (to identify an alternative diagnosis for children who may be misdiagnosed as having TB), adverse events and deterioration in the clinical condition.

4.3. Consolidated recommendations on TB diagnostics and diagnostic approaches relevant to children and adolescents

Table 5: WHO recommendations on diagnostic approaches relevant to children and adolescents

WHO consolidated guidelines on tuberculosis. Module 3: diagnosis – rapid diagnostics for tuberculosis detection, 2021 update *(16)*
Recommendations on Xpert MTB/RIF and Xpert Ultra as initial tests in adults and children with signs and symptoms of pulmonary TB (Note that in these guidelines, adults refer to persons aged 15 years and above and children aged below 15 years, therefore the adult population includes older adolescents):
In adults* with signs and symptoms of pulmonary TB, Xpert MTB/RIF should be used as an initial diagnostic test for TB and rifampicin-resistance detection in sputum rather than smear microscopy/culture and phenotypic drug susceptibility testing (DST).   *(Strong recommendation, high certainty of evidence for test accuracy; moderate certainty of evidence for patient-important outcomes)*   ** Adults and adolescents from 15 years*
In children with signs and symptoms of pulmonary TB, Xpert MTB/RIF should be used as an initial diagnostic test for TB and rifampicin-resistance detection in sputum, gastric aspirate, nasopharyngeal aspirate and stool rather than smear microscopy/culture and phenotypic DST.   *(Strong recommendation, moderate certainty for accuracy in sputum; low certainty of evidence for test accuracy in gastric aspirate, nasopharyngeal aspirate and stool)*
In adults* with signs and symptoms of pulmonary TB and without a prior history of TB (≤5 years) or with a remote history of TB treatment (>5 years since end of treatment), Xpert Ultra should be used as an initial diagnostic test for TB and for rifampicin-resistance detection in sputum, rather than smear microscopy/culture and phenotypic DST.   *(Strong recommendation, high certainty of evidence for test accuracy)*   ** Adults and adolescents from 15 years*
In adults* with signs and symptoms of pulmonary TB and with a prior history of TB and an end of treatment within the last 5 years, Xpert Ultra may be used as an initial diagnostic test for TB and for rifampicin-resistance detection in sputum, rather than smear microscopy/culture and phenotypic DST.   *(Conditional recommendation, low certainty of evidence for test accuracy)*   ** Adults and adolescents from 15 years*
Recommendations on Xpert MTB/RIF and Xpert Ultra as initial tests in adolescents and children with signs and symptoms of extrapulmonary TB
In adults and children with signs and symptoms of TB meningitis, Xpert MTB/RIF or Xpert Ultra should be used in cerebrospinal fluid (CSF) as an initial diagnostic test for TB meningitis rather than smear microscopy/culture.   *(Strong recommendation, moderate certainty of evidence for test accuracy for Xpert MTB/RIF; low certainty of evidence for test accuracy for Xpert Ultra)*

In adults and children with signs and symptoms of extrapulmonary TB, Xpert MTB/RIF may be used in lymph node aspirate, lymph node biopsy, pleural fluid, peritoneal fluid, pericardial fluid, synovial fluid or urine specimens as the initial diagnostic test for respective form of extrapulmonary TB rather than smear microscopy/culture.

(Conditional recommendation, moderate certainty of evidence for test accuracy for pleural fluid; low certainty for lymph node aspirate, peritoneal fluid, synovial fluid, urine; very low certainty for pericardial fluid, lymph nodes biopsy)

In adults and children with signs and symptoms of extrapulmonary TB, Xpert Ultra may be used in lymph node aspirate and lymph node biopsy as the initial diagnostic test for lymph nodes TB rather than smear microscopy/culture.

(Conditional recommendation, low certainty of evidence)

In adults and children with signs and symptoms of extrapulmonary TB, Xpert MTB/RIF or Xpert Ultra should be used for rifampicin-resistance detection rather than culture and phenotypic DST.

(Strong recommendation, high certainty of evidence for test accuracy for Xpert MTB/RIF; low certainty of evidence for Xpert Ultra)

In HIV-positive adults and children with signs and symptoms of disseminated TB, Xpert MTB/RIF may be used in blood, as an initial diagnostic test for disseminated TB.

(Conditional recommendation, very low certainty of evidence for test accuracy)

Recommendations on Xpert MTB/RIF and Xpert Ultra repeated testing in children and adolescents with signs and symptoms of pulmonary TB

In adults* with signs and symptoms of pulmonary TB who have an Xpert Ultra trace positive result on the initial test, repeated testing with Xpert Ultra may not be used.

(Conditional recommendation, very low certainty of evidence for test accuracy)

Remark: *Xpert Ultra trace results in adolescents will require follow-up, including reassessing clinical symptoms and information on prior history of TB. In the case of suspected rifampicin resistance, repeated testing may provide additional benefit for detection as well as an initial attempt to assess rifampicin resistance. For interpretation of trace results in children, see section 4.1.3.*

* Adults and adolescents from 15 years

In children with signs and symptoms of pulmonary TB in settings with pretest probability below 5% and an Xpert MTB/RIF negative result on the initial test, repeated testing with Xpert MTB/RIF in sputum, gastric fluid, nasopharyngeal aspirate or stool specimens may not be used.

(Conditional recommendation, low certainty of evidence for test accuracy for sputum; and very low for other specimen types)

In children with signs and symptoms of pulmonary TB in settings with pretest probability 5% or more and an Xpert MTB/RIF negative result on the initial test, repeated testing with Xpert MTB/RIF (for total of two tests) in sputum, gastric fluid, nasopharyngeal aspirate and stool specimens may be used.

(Conditional recommendation, low certainty of evidence for test accuracy for sputum; and very low for other specimen types)

In children with signs and symptoms of pulmonary TB in settings with pretest probability below 5% and an Xpert Ultra negative result on the initial test, repeated testing with Xpert Ultra in sputum or nasopharyngeal aspirate specimens may not be used.

(Conditional recommendation, very low certainty of evidence for test accuracy)

In children with signs and symptoms of pulmonary TB in settings with pretest probability 5% or more and an Xpert Ultra negative result on the first initial test, repeated one Xpert Ultra test (for a total of two tests) in sputum and nasopharyngeal aspirate specimens may be used.

(Conditional recommendation, very low certainty of evidence for test accuracy)

Recommendations on Xpert MTB/RIF and Xpert Ultra as initial tests for pulmonary TB in adults in the general population either with signs and symptoms of TB or chest radiograph with lung abnormalities or both

In adults* in the general population who had either signs or symptoms of TB or chest radiograph with lung abnormalities or both, the Xpert MTB/RIF or Xpert Ultra may replace culture as the initial test for pulmonary TB.

(Conditional recommendation, low certainty of the evidence in test accuracy for Xpert MTB/RIF; and moderate certainty for Xpert Ultra)

* Adults and adolescents from 15 years

In adults* in the general population who had either a positive TB symptom screen or chest radiograph with lung abnormalities or both, one Xpert Ultra test may be used rather than two Xpert Ultra tests as the initial test for pulmonary TB.

(Conditional recommendation, very low certainty of evidence for test accuracy).

* Adults and adolescents from 15 years

Truenat MTB, MTB Plus and Truenat MTB-RIF Dx in adults and children with signs and symptoms of pulmonary TB (specimen type: sputum)

In children and adults* with signs and symptoms of pulmonary TB, the Truenat MTB or MTB Plus may be used as an initial diagnostic test for TB rather than smear microscopy/culture.

(Conditional recommendation, moderate certainty of evidence for test accuracy)

* Adults and adolescents from 15 years

In children and adults* with signs and symptoms of pulmonary TB and a Truenat MTB or MTB Plus positive result, Truenat MTB-RIF Dx may be used as an initial test for rifampicin resistance rather than culture and phenotypic DST.

(Conditional recommendation, very low certainty of evidence for test accuracy)

* Adults and adolescents from 15 years

Moderate complexity automated nucleic acid amplification tests (NAATs) for detection of TB and resistance to rifampicin and isoniazid

In people with signs and symptoms of pulmonary TB, moderate complexity automated NAATs may be used on respiratory samples for the detection of pulmonary TB, and of rifampicin and isoniazid resistance, rather than culture and phenotypic DST.

(Conditional recommendation, moderate certainty of evidence for diagnostic accuracy)

Loop-mediated isothermal amplification

TB-LAMP may be used as a replacement test for sputum-smear microscopy for diagnosing pulmonary TB in adults* with signs and symptoms consistent with TB.

(Conditional recommendation, very low certainty evidence)

* Adults and adolescents from 15 years

TB-LAMP may be used as a follow-on test to smear microscopy in adults* with signs and symptoms consistent with pulmonary TB, especially when further testing of sputum smear-negative specimens is necessary.

(Conditional recommendation, very low certainty evidence)

* Adults and adolescents from 15 years

Lateral flow urine lipoarabinomannan assay

In inpatient settings, WHO strongly recommends using LF-LAM to assist in the diagnosis of TB disease in HIV-positive adults and children:

a. with signs and symptoms of TB (pulmonary and/or extrapulmonary) *(strong recommendation, moderate certainty in the evidence about the intervention effects)* or

b. with advanced HIV disease or who are seriously ill *(strong recommendation, moderate certainty in the evidence about the intervention effects)*; or

c. irrespective of signs and symptoms of TB and with a CD4 cell count of less than 200 cells/mm^3 *(strong recommendation, moderate certainty in the evidence about the intervention effects)*.

In outpatient settings, WHO suggests using LF-LAM to assist in the diagnosis of TB disease in HIV-positive adults and children:

a. with signs and symptoms of TB (pulmonary and/or extrapulmonary) or seriously ill *(conditional recommendation, low certainty in the evidence about test accuracy)*; and

b. irrespective of signs and symptoms of TB and with a CD4 cell count of less than 100 cells/mm^3 *(conditional recommendation, very low certainty in the evidence about test accuracy)*

In outpatient settings, WHO recommends **against** using LF-LAM to assist in the diagnosis of TB disease in HIV-positive adults and children:

a. without assessing TB symptoms *(strong recommendation, very low certainty in the evidence about test accuracy)*;

b. without TB symptoms and unknown CD4 cell count or without TB symptoms and CD4 cell count greater than or equal to 200 cells/mm^3 *(strong recommendation, very low certainty in the evidence about test accuracy)*; and

c. without TB symptoms and with a CD4 cell count of 100–200 cells/mm^3 *(conditional recommendation, very low certainty in the evidence about test accuracy)*.

Low complexity NAATs for detection of resistance to isoniazid and second-line TB agents

In people with bacteriologically confirmed pulmonary TB, low complexity automated NAATs may be used on sputum for the initial detection of resistance to isoniazid and fluoroquinolones, rather than culture-based phenotypic DST.

(Conditional recommendation, moderate certainty of evidence for diagnostic accuracy)

In people with bacteriologically confirmed pulmonary TB and resistance to rifampicin, low complexity automated NAATs may be used on sputum for the initial detection of resistance to ethionamide, rather than DNA sequencing of the *inhA* promoter.

(Conditional recommendation, very low certainty of evidence for diagnostic accuracy)

In people with bacteriologically confirmed pulmonary TB and resistance to rifampicin, low complexity automated NAATs may be used on sputum for the initial detection of resistance to amikacin, rather than culture-based phenotypic DST.

(Conditional recommendation, low certainty of evidence for diagnostic accuracy)

First-line line-probe assay (LPAs)

For persons with a sputum smear-positive specimen or a cultured isolate of *Mycobacterium tuberculosis* complex (MTBC), commercial molecular LPAs may be used as the initial test instead of phenotypic culture-based DST to detect resistance to rifampicin and isoniazid.

(Conditional recommendation, moderate certainty in the evidence for the test's accuracy)

Second-line line-probe assays (SL-LPAs)

For patients with confirmed MDR/RR-TB, SL-LPA may be used as the initial test, instead of phenotypic culture-based DST, to detect resistance to fluoroquinolones.

(Conditional recommendation, moderate certainty in the evidence for test accuracy for direct testing of sputum specimens; low certainty in the evidence for test accuracy for indirect testing of Mycobacterium tuberculosis cultures)

For patients with confirmed MDR/RR-TB, SL-LPA may be used as the initial test, instead of phenotypic culture-based DST, to detect resistance to the second-line injectable drugs.

(Conditional recommendation, low certainty in the evidence for test accuracy for direct testing of sputum specimens; very low certainty in the evidence for test accuracy for indirect testing of Mycobacterium tuberculosis cultures)

High complexity reverse hybridization-based NAATs for detection of pyrazinamide resistance

In people with bacteriologically confirmed TB, high complexity reverse hybridization-based NAATs may be used on *M. tuberculosis* culture isolates for detection of pyrazinamide resistance rather than culture-based phenotypic DST.

(Conditional recommendation, very low certainty of evidence for diagnostic accuracy)

Commercial serodiagnostic tests for diagnosis of tuberculosis: policy statement, 2011 *(17)*

Commercial serodiagnostics should not be used in children suspected of active pulmonary or extrapulmonary TB, irrespective of their HIV status.

(Strong recommendation, very low certainty of evidence for the use of commercial serodiagnostics)

5. Treatment of TB disease in children and adolescents

This chapter contains four new recommendations (published for the first time and described in full detail here) relevant to the treatment of TB disease in children and adolescents as well as other valid WHO recommendations that apply to the treatment of TB in children and adolescents (section 5.4). The four new recommendations concern drug-susceptible TB (DS-TB): (i) a four-month regimen for children and adolescents below 16 years of age with non-severe drug-susceptible TB (section 5.1); (ii) a six-month intensive regimen to treat TBM composed of isoniazid, rifampicin, pyrazinamide and ethionamide (section 5.2); (iii) use of bedaquiline as part of shorter or longer regimens for children of all ages to treat MDR/RR-TB (section 5.3.1); and (iv) use of delamanid as part of longer regimens for children of all ages to treat MDR/RR-TB (section 5.3.2).

The recommendations in this chapter have been consolidated from current WHO guidelines on TB treatment, namely the *WHO consolidated guidelines on tuberculosis. Module 4: treatment – drug-susceptible tuberculosis treatment, 2022 update (55)* and the *WHO consolidated guidelines on tuberculosis. Module 4: treatment – drug-resistant tuberculosis treatment, 2020 update (9)*. Where appropriate, details on recommendations from the 2014 *Guidance for national tuberculosis programmes on the management of tuberculosis in children (second edition) (8),* and *Rapid advice: treatment of tuberculosis in children (56)*, which remain relevant have been included. For more information on each recommendation including the remarks, source of evidence, justification, subgroup, implementation and monitoring and evaluation considerations, the source guidelines or WHO TB KSP should be consulted.

5.1. Treatment shortening in children and adolescents with non-severe TB

Recommendation:

In children and adolescents between 3 months and 16 years of age with non-severe TB (without suspicion or evidence of MDR/RR-TB), a 4-month treatment regimen (2HRZ(E)/2HR) should be used.

(Strong recommendation, moderate certainty of evidence)

Remarks

- Non-severe TB is defined as: Peripheral lymph node TB; intrathoracic lymph node TB without airway obstruction; uncomplicated TB pleural effusion or paucibacillary, non-cavitary disease, confined to one lobe of the lungs, and without a miliary pattern.

- Children and adolescents who do not meet the criteria for non-severe TB should receive the standard six-month treatment regimen (2HRZE/4HR), or recommended treatment regimens for severe forms of extrapulmonary TB.

- The use of ethambutol in the first two months of treatment is recommended in settings with a high prevalence of HIV,[26] or of isoniazid resistance.[27]

5.1.1. Justification and evidence

The majority of children with TB have less severe forms of the disease than adults. Treatment regimens that are shorter than those for adults may be effective in treating children with TB, however solid evidence to substantiate this has been lacking to date. Shorter treatment regimens can result in lower costs to families and health services, potentially less toxicity, lower risks of drug-drug interactions in children living with HIV, and fewer problems with adherence. Shorter, safe and effective treatment regimens for children with both drug-susceptible and DR-TB benefit children with TB and their families, and are a key intervention to achieve the End TB Strategy targets, as well as targets related to children set during the UNGA High-Level Meeting on the fight against tuberculosis in 2018. New evidence from a recently completed trial on the shortened treatment of drug-susceptible TB in children and adolescents has paved the way for new recommendations on shorter regimens for this group.

The SHINE trial (Shorter Treatment for Minimal Tuberculosis in Children) was the first and only large phase three trial to evaluate the duration of TB treatment in children with non-severe drug-susceptible TB. Therefore, evidence from the trial rather than a systematic review, was used to answer this PICO question *(57)*. The SHINE trial was a multi-centre, open-label, parallel-group, non-inferiority, randomized, controlled, two-arm trial comparing 4-month (16 weeks) versus the standard 6-month (24 weeks) treatment durations in children under 16 years of age with symptomatic non-severe TB. Children and young adolescents aged below 16 years were treated with rifampicin, isoniazid, pyrazinamide with or without ethambutol using WHO recommended doses, appropriate for paediatric dosing *(58)*.

PICO question: In children and adolescents with non-severe TB, should a 4-month intervention regimen versus the standard 6-month regimen conforming to WHO guidelines be used?

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[26] Defined as countries, subnational administrative units, or selected facilities, where the HIV prevalence among adult pregnant women is ≥1% or among TB patients is ≥5% in the 2014 *Guidance for national tuberculosis programmes on the management of tuberculosis in children (second edition) (8)*.

[27] WHO does not intend to establish thresholds for low, moderate or high levels of prevalence of isoniazid resistance; NTPs will establish definitions for their own countries.

Evidence: In the SHINE trial, the primary efficacy outcome was a composite of treatment failure (including an extension of treatment beyond the replacement of missed doses, TB treatment drug changes or restarts due to suspected treatment failure), on-treatment loss-to-follow-up, TB recurrence or death by 72 weeks (from randomization), excluding children not reaching 16 weeks follow-up (modified-intention-to-treat). The non-inferiority margin for the primary efficacy outcome was 6%. The primary safety outcome was grade 3–5 adverse events recorded while on TB treatment.

The SHINE trial definition of non-severe TB was: peripheral lymph node TB or respiratory TB (including uncomplicated intrathoracic lymph node disease) confined to one lobe without cavities, no significant airway obstruction, uncomplicated pleural effusion, and no miliary TB.

The SHINE trial inclusion criteria were: children and young adolescents aged <16 years; weight ≥3 kg; no known drug resistance; symptomatic but non-severe TB; smear negative on gastric aspirate or other respiratory sample (an Xpert MTB/RIF positive, rifampicin susceptible result was allowed);[28] clinician's decision to treat with a standard first-line regimen; not treated for TB in the previous two years; known HIV status (positive or negative). Trial exclusion criteria were: respiratory sample acid fast bacilli smear-positive (a smear-positive peripheral lymph node sample was allowed); premature birth (<37 weeks) and aged under 3 months; miliary TB, spinal TB, TBM, osteoarticular TB, abdominal TB, congenital TB; pre-existing, non-tuberculous disease likely to prejudice the response to, or assessment of, treatment (such as liver or kidney disease, peripheral neuropathy or cavitation); any known contraindication to taking TB drugs; known contact with a drug-resistant adult source case (including mono-resistant TB); known drug-resistance in the child; being severely ill; pregnancy.

A total of 1204 children were enrolled in the trial between July 2016 and July 2018. The median age of enrolled children was 3.5 years (range: 2 months – 15 years), 52% were male, 11% had HIV-infection, and 14% had bacteriologically confirmed TB. Retention in the trial by 72 weeks and adherence[29] to allocated TB treatment were 95% and 94%, respectively. Sixteen (2.8%) versus 18 (3.1%) children reached the primary efficacy outcome (treatment failure) in the 16- versus 24-week arms respectively, with an unadjusted difference of -0.3% (95% CI: -2.3, 1.6). Treatment success was reported in 97.1% of participants receiving the 16-week regimen versus 96.9% in those receiving the 24-week regimen (relative risk (RR): 1.00, 95% CI: 0.98–1.02). Non-inferiority of the 16-week regimen was consistent across all intention-to-treat, per-protocol and key secondary analyses. This included restricting the analysis to the 958 (80%) children that were independently adjudicated to have TB at baseline by the trial Endpoint Review Committee. A total of 7.8% of children experienced a grade 3–5 adverse event in the 16-week arm, versus 8.0% in the 24-week arm (RR: 0.98, 95% CI: 0.67–1.44). There were 115 on-treatment grade ≥3 adverse events in 95 (8%) children, 47 (8%) in the 16-week and 48 (8%) in the 24-week arm, most common being pneumonia or other chest infections (29 (25%)) or liver-related events (11 (10%)) across both arms. There were 17 grade 3 or 4 adverse reactions (considered possibly, probably or definitely) related to trial drugs, including 11 hepatic events; all adverse reactions except three occurred in the first eight weeks of treatment.

GDG considerations: The GDG judged that while the desirable effects related to this PICO question are related to treatment outcomes, shortening the duration of treatment is also important and desirable (as reducing the length of treatment could make treatment easier for children and caregivers as well as reduce cost for families and the health system). The GDG discussed that since the SHINE trial was a non-inferiority trial, no difference in unfavourable outcomes between the two arms is what the trial aimed to detect. Therefore, both desirable and undesirable effects were judged by most GDG members as trivial. Since non-inferiority of the 4-month regimen was demonstrated in the trial, the balance of effects was judged to not favour either the shorter or the longer duration of treatment.

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[28] In the SHINE trial, children with Xpert MTB/RIF results had very low or low semi-quantitative results, or a negative result. Xpert Ultra was not used in the SHINE trial.

[29] In the SHINE trial, adherence was defined as the proportion of children who received an adequate amount of treatment (as defined in the statistical analysis plan for both the intervention and control regimens; generally, a cut off of 80% of the allocated doses was used, within a certain time frame of starting each phase of treatment (i.e. intensive phase versus continuation phase).

However, the GDG noted that treatment duration is a critical issue which was further considered in the context of issues such as cost, acceptability and feasibility.

The GDG also discussed that presumably, a shorter duration of treatment would reduce costs to both the health care system and to children with TB and their families. The GDG ultimately agreed on 'moderate savings' despite the varying views on the level of these savings. The GDG judged that equity was probably increased with a shorter duration of treatment. Despite no direct evidence on acceptability, the GDG judged that the shorter regimen was acceptable to stakeholders.

In addition, the GDG felt that, in the absence of exposure to DR-TB, access to CXR would help distinguish between non-severe and severe disease. However, the panel recognized that access to CXR is often limited or quality of CXR and capacity for interpretation is insufficient at lower levels of the health care system, which may have equity implications. Therefore, feasibility was judged to vary by setting. The GDG noted that it is critically important to clearly define "non-severe" disease and that NTPs be encouraged to scale up access to quality CXR and train health care providers in its interpretation. Overall, the GDG judged that if the severity of TB disease in children can be adequately determined under programmatic conditions, then implementation of a 4-month regimen is highly feasible.

5.1.2. Subgroup considerations

Children with peripheral lymph node TB: Although the number of children with peripheral lymph node TB in the SHINE trial were small (N=19 in the 16-week arm and N=21 in the 24-week arm), there was no difference in the proportion of unfavourable outcomes between the two arms. The SHINE trial also found that 16 weeks of treatment was non-inferior compared to 24 weeks of treatment among children with both peripheral lymph node disease and pulmonary disease (N=182 in the 16-week arm and N=171 in the 24-week arm). These results may provide reassurance to clinicians regarding a seemingly delayed clinical response to TB treatment, frequently seen in children with peripheral lymph node TB (where lymph nodes remain enlarged even after treatment).

Children and adolescents living with HIV infection (CALHIV): CALHIV were eligible for enrolment in the SHINE trial; 65 (11%) CALHIV were enrolled in the 16-week arm and 62 (10%) in the 24-week arm. 49% of CALHIV in the 16-week arm and 43% in the 24-week arm were on antiretroviral treatment at the time of enrolment. 20% of CALHIV in both arms had a CD4 count of less than 200 cells per mm[3]. 51% of CALHIV in the 16-week arm and 63% in the 24-week arm were classified as severe as per the WHO immunological classification for established HIV infection *(59)*. In this subgroup, the 16-week regimen was non-inferior as compared to the 24-week regimen, although the 95% confidence interval for the risk difference was wide (risk difference -4.3, 95% CI -14.9 to 6.2).

In view of the limited evidence, clinicians may consider treating CALHIV with non-severe TB for 4 months, depending on the degree of immunosuppression and ART status, as well as the presence of other opportunistic infections. These children and adolescents will need to be monitored closely, especially at 4 months of treatment, and treatment extended to 6 months if there is insufficient progress.

Children with SAM: In the SHINE trial, SAM was defined as weight-for-height Z-score (WHZ) < −3 or MUAC <115 mm *(60)*. Thirty children with SAM (5%) were included in the 16-week arm and 33 (5%) in the 24-week arm. No separate subgroup analysis was therefore conducted for children with SAM.

In view of the insufficient evidence on this subgroup, and as SAM is defined as a danger sign, children with SAM and non-severe TB should preferably receive 6 months of TB treatment.

Infants <3 months of age and/or weighing <3 kg: Infants <3 months of age and infants weighing <3 kg (including premature birth (<37 weeks) were not eligible for inclusion in the SHINE trial. No new data on the treatment of congenital TB and very young infants (aged 0–3 months) with TB

disease was received following a call for data. Therefore, infants aged 0–3 months with suspected or confirmed PTB or tuberculous peripheral lymphadenitis should be promptly treated with the 6-month treatment regimen (2HRZ(E)/4HR), as per the existing recommendation from the 2014 *Guidance for national tuberculosis programmes on the management of tuberculosis in children (second edition) (8)*. Treatment may require dose adjustment to reconcile the effect of age and possible toxicity in young infants. The decision to adjust doses should be taken by a clinician experienced in the management of paediatric TB.

Children treated for TB in the past two years: Given the increased risk of treatment failure and of drug resistance, children and adolescents treated in the preceding two years were not eligible for inclusion in the SHINE trial; they should be treated with the 6-month treatment regimen (2HRZ(E)/4HR).

5.1.3. Implementation considerations

Assessing severity of disease: The feasibility of assessing the severity of TB disease, particularly in settings without access to CXR or capacity for CXR interpretation and WHO-recommended diagnostic tests was identified as a major implementation consideration. Chest radiography was identified by the GDG as a critical tool to evaluate the severity of intrathoracic disease. As indicated under the recommendation remarks, non-severe intrathoracic or PTB disease refers to: intrathoracic lymph node TB without airway obstruction; uncomplicated TB pleural effusion or paucibacillary, non-cavitary disease confined to one lobe of the lungs and without a miliary pattern. Extensive or advanced disease in children under 15 years of age is usually defined by the presence of cavities or bilateral disease on CXR *(61)*. NTPs are encouraged to scale up access to quality CXR and provide training to health care providers in its interpretation. Out-of-pocket expenses for CXR pose a potential barrier to TB diagnosis and access to shorter regimen for eligible children and young adolescents. In the SHINE trial, children who were Xpert MTB/RIF positive, but sputum smear-negative were eligible for inclusion. The 85 children (7%) who were Xpert MTB/RIF positive (45 in the 4-month arm and 40 in the 6-month arm), had very low or low semi-quantitative Xpert MTB/RIF results.

Detailed implementation guidance is provided in the *Operational handbook on the management of tuberculosis in children and adolescents*, taking into consideration differences in the health care system and country context, including the availability of diagnostic tools to make a diagnosis and to assess disease severity. While access to CXR is an important implementation consideration, it should not be a barrier for children and adolescents in lower resourced settings to benefit from the shorter regimen. The implementation guidance in the operational handbook comprises criteria for assessing disease severity, including clinical criteria in the absence of CXR or rapid diagnostics or other bacteriological tests, to determine eligibility for the shorter regimen. Children with Xpert MTB/RIF or Ultra results that are trace, very low or low, who meet radiographical or clinical criteria for non-severe TB, can be treated with the 4-month regimen.

Continuum between TB infection and disease: An additional implementation consideration is the concept that a continuum exists between TB infection, non-severe and more severe forms of TB disease in children. Shorter treatment regimens for drug-susceptible TB are now very similar to recently recommended shorter regimens for the treatment of TB infection, in terms of duration and composition, in particular the regimen that consists of 3 months of daily isoniazid and rifampicin (3HR) *(14)*. This implies that incorrectly diagnosing a child who has TB infection as having non-severe TB disease may not have severe consequences.

Contact investigation: Another implementation consideration is the scale-up of contact investigation approaches, which can improve early identification of children with non-severe disease who may benefit from the 4-month regimen.

Use of ethambutol in the intensive phase of treatment: Children and young adolescents with non-severe TB who live in settings with low HIV prevalence or a low prevalence of isoniazid resistance and those who are HIV negative can be treated with a three-drug regimen (HRZ) for 2 months, followed

by 2 months of HR. Children and young adolescents with non-severe TB who are living in settings where the prevalence of HIV is high[30] and/or the prevalence of isoniazid resistance is high[31] should be treated with HRZE for 2 months followed by HR for 2 months. In the SHINE trial, ethambutol was used in line with these recommendations as per national guidelines and all CALHIV received ethambutol as part of their treatment. For the 6-month regimen used to treat more severe forms of TB, it is recommended to add ethambutol to the regimen (i.e. 4HRZE/2HR).

Child-friendly formulations: NTPs are encouraged to prioritize the use of child-friendly fixed dose combination (FDC) formulations for TB treatment in children up to 25 kg body weight, such as: the 3-FDC HRZ 50/75/150 mg with or without the addition of dispersible ethambutol, and the 2-FDC HR 50/75 mg (available from the Stop TB Partnership Global Drug Facility (GDF)). Capacity building of health care workers at all levels of the health system on diagnostic approaches (including treatment decision algorithms), eligibility for the four-month regimen and monitoring of children on first-line TB treatment will also be critical factors in the successful implementation of the shorter regimen.

Treatment of severe PTB in children and young adolescents: Children and young adolescents with forms of PTB that do not meet the eligibility criteria for the four-month regimen should be treated with a standard 6-month regimen that includes a fourth drug (ethambutol) in the intensive phase (such as 2HRZE/4HR).

Treatment options for adolescents from 12 years of age: Another implementation consideration is that adolescents aged 12 years and above with TB can benefit from the 4-month regimen that consists of isoniazid, rifapentine, moxifloxacin and pyrazinamide (HPMZ), which is now conditionally recommended by WHO *(55)*. Adolescents aged between 12 and 16 years therefore have three options for treatment: the 4-month HPMZ regimen, the 4-month 2HRZ(E)/2HR regimen, and the standard 6-month 2HRZ(E)/4HR regimen. Adolescents from 16 years of age were not included in the SHINE trial and therefore have two options: the 4-month HPMZ regimen and the standard 6-month 2HRZE/4HR regimen.

Choosing an appropriate regimen for this age group will depend on clinical factors (such as the presence of severe disease or if living with HIV, ART status and CD4 count) as well as contextual factors (including the availability of the HPMZ regimen in the country).

5.1.4. Monitoring and evaluation

The clinical monitoring requirements for the shorter regimen remain the same as for the 6-month regimen and treatment outcomes are determined at the end of the 4-month regimen.

Should there be insufficient clinical improvement after completion of the 4-month regimen, the clinician may decide to extend treatment to 6 months while considering alternative diagnoses, including DR-TB.

Monitoring for potential relapse is a priority for shorter regimens especially when they are introduced into programmatic settings. Therefore, follow-up of children and young adolescents for up to 12 months after completion of the 4-month regimen is important.

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[30] This level of resistance was defined as countries, subnational administrative units, or selected facilities, where the HIV prevalence among adult pregnant women is ≥1% or among TB patients is ≥5% in the 2014 *Guidance for national tuberculosis programmes on the management of tuberculosis in children (second edition) (8)*.

[31] WHO does not intend to establish thresholds for low, moderate or high levels of prevalence of isoniazid resistance; instead NTPs will establish definitions for their own countries.

5.2. Treatment regimens for TB meningitis in children and adolescents

Recommendation

In children and adolescents with bacteriologically confirmed or clinically diagnosed TB meningitis (without suspicion or evidence of MDR/RR-TB), a 6-month intensive regimen (6HRZEto) may be used as an alternative option to the 12-month regimen (2HRZE/10HR)

(Conditional recommendation, very low certainty of the evidence).

Remarks

- The shorter intensive regimen is suitable for children and adolescents who have no evidence of drug resistance and in children and adolescents who have a low likelihood of drug-resistant TB, e.g. those without risk factors for any form of drug-resistant TB.

- The recommendation from the *Guidance for national tuberculosis programmes on the management of tuberculosis in children (second edition, 2014)* remains an option for the treatment of children and adolescents with suspected or confirmed TB meningitis (TBM): Children and adolescents with suspected or confirmed tuberculous meningitis should be treated with a four-drug regimen (HRZE) for 2 months, followed by a two-drug regimen (HR) for 10 months, the total duration of treatment being 12 months *(Strong recommendation, low certainty of evidence).*

- Due to a lack of data, the shorter intensive treatment regimen recommendation should not be used in children and adolescents living with HIV who are diagnosed with TB meningitis.

5.2.1. Justification and evidence

Following *M. tuberculosis* infection, young children are at high risk of developing the most severe forms of the disease, of which the most devastating form is TBM. This predominantly affects young children with a peak age of onset of 2–4 years *(2)*. Up to 15% of childhood TB may present as TBM *(62)*; with a decreasing incidence of bacterial meningitis attributed to other causes, TB is the leading cause of bacterial meningitis in many settings *(63)*. TBM is associated with significant mortality and morbidity; in a systematic review and meta-analysis published in 2014, the risk of death among children aged 0–14 years with TBM was estimated at 19.3% and the risk of neurological sequelae among TBM survivors was estimated at 36.7% *(64)*. Even among children without severe neurological sequelae, attention deficit and behavioural disorders are common and the human cost and financial burden for families and society are high. Diagnosis in the most advanced clinical stage, which occurred in almost 50% of children with TBM, was associated with worse outcomes based on the findings of the review. WHO currently recommends a regimen of 12 months duration to treat TBM, consisting of isoniazid, rifampicin, ethambutol and pyrazinamide given daily for the first 2 months, followed by isoniazid and rifampicin given daily for 10 additional months (2HRZE/10HR) *(8, 56)*. Recommended doses to be used in this regimen are the same as those for the treatment of PTB *(8)*.

The recommendation on the use of the 12-month regimen was based on a literature review *(65)* and was first included in the *2010 Rapid advice: treatment of TB in children (56)*. This review included 46 studies with information on the efficacy of different regimens and dosages for the management of TBM (25 studies included paediatric data and 21 included data on both adults and children). The majority of these studies were non-randomized, non-comparative studies. The quality of the studies ranged from low to very low and no clear conclusions could be drawn from the efficacy studies, given that they differed widely in terms of design, drugs used and patient populations. None of the studies from this review were entered into GRADE, given the lack of comparative data.

Shorter regimens to treat paediatric TBM are used in some settings. The South African National TB Guidelines recommend a regimen composed of daily isoniazid, rifampicin, pyrazinamide and

ethionamide, given for 6 months (6HRZEto) *(66)*. The recommendations in South Africa are based on expert opinion, in particular with regards to replacing ethambutol with a drug (ethionamide) that has more efficient blood-brain barrier penetration *(65)*. A clinical trial is underway to compare a regimen consisting of higher-dose isoniazid, higher-dose rifampicin, pyrazinamide and levofloxacin given daily for 6 months, compared to the WHO-recommended regimen, but the results are not expected until 2023 (SURE trial, ISRCTN40829906). Shorter regimens may be as effective and safe, and may improve adherence and reduce the burden on persons with TBM and health care systems, but it is not known how outcomes compare between the shorter regimens and the WHO-recommended 12-month regimen.

PICO question: In children and adolescents with presumed or bacteriologically confirmed drug-susceptible TB meningitis, should a 6-month intensive regimen, compared to the 12-month regimen that conforms to WHO guidelines be used?

Evidence: To inform recommendations on the treatment for child and adolescent TBM, a systematic review and meta-analysis was conducted to compare the effectiveness of shorter regimens versus the current WHO-recommended 12-month regimen *(8)*. The primary intervention of interest was the regimen currently used in South Africa *(66)*; in secondary analyses, outcomes associated with other shorter regimens were examined. The search criteria from an earlier systematic review and meta-analysis conducted in 2014 were updated and the search was run in February 2021 *(64)*. Studies with available information on at least the composition and duration of treatment regimens were included. Ineligible regimens included those without rifampicin, treatment regimens with a duration over 12 months other than the WHO regimen, intermittent regimens and non-intensive short regimens. Pooled proportions were estimated across studies and within regimens through aggregate-level meta-analysis using GLMM with Gauss-Hermite quadrature for the following outcomes: death by end of treatment; loss to follow-up; treatment success; neurological sequelae (among survivors); and survival without neurological sequelae (among those starting treatment). Subgroup analyses were planned but were not feasible, due to insufficient data.

Of the 1820 unique citations screened, 149 full text papers were evaluated. Of these, five met inclusion criteria for the systematic review. In addition, two unpublished cohorts were eligible for inclusion. In total, four studies of intervention regimens (three published and one unpublished) *(67–70)*, and three studies of the comparator regimen (two published and one unpublished) *(71–73)* were identified. No studies performing head-to-head comparisons of regimens were identified. Three of the four studies of intervention regimens were conducted in a single referral centre in South Africa. As only one study reported on outcomes from an 8-month regimen in Vietnam *(69)*, it was excluded from the meta-analysis. The two published studies of the comparator regimen were conducted at different sites in India *(71, 72)*, while data for the unpublished study were collected in various centres in Europe through the Pediatric Tuberculosis Network European Trials Group (ptbnet) *(73)*. A total of 837 patients with TBM received intervention regimens with the median age in each study ranging from 2.3 to 5.5 years (age range: 2 months to 15 years). Among the 282 patients treated with the comparator regimen, the median age in the European study was 3.3 years, while summary data on age were not reported in the studies from India.

The cumulative number of deaths was recorded at the end of treatment for each regimen (i.e. at 6 months after treatment initiation in studies of the intervention regimen; at 12 months after treatment initiation in studies of the comparator regimen). Among studies of the intervention regimen, 0.0%–9.6% of patients died within six months; most deaths occurred early after hospital admission and primarily involved patients diagnosed in stage 3 at baseline. Among studies of the comparator regimen (i.e. the standard of care), 7.1%–30.0% of patients died. In one of these studies, diagnosis at stage 3 was most strongly associated with mortality, although stage-specific outcome data were not reported. In a random effects meta-analysis, the pooled proportions of deaths were 6.0% (95% confidence interval [CI] 2.0–13.0) and 24.0% (95% CI: 18.0–32.0) for children and adolescents who received the intervention and comparator regimens, respectively. The percentage of patients with

treatment success were 78.5%–100.0%, with a random effects pooled proportion of 95.0% (95% CI: 74.0–99.0) among studies of the intervention regimen, and 70%–85.7%, with a random effects pooled proportion of 75.0% (95% CI: 69.0–81.0) among studies of the comparator regimen. Neurological sequelae were defined and assessed differently across studies. Among patients treated with the intervention regimen, 50.0%–66.7% had neurological sequelae, mostly categorized as mild. The vast majority of these were among patients diagnosed at stage 2 or 3. Among patients treated with the comparator regimen, 31.9%–50.0% had neurological sequelae. In one study on the comparator regimen from India, 17 of 29 (58.6%) cases were categorized as mild. The random effects pooled proportions of neurological sequelae among survivors were 66.0% (95% CI: 55.0–75.0) and 36.0% (95% CI: 30.0–43.0) for the intervention and comparator regimens, respectively. Among the 135 HIV-negative and 13 HIV-positive patients who received the intervention regimen in South Africa, none relapsed within two years of post-treatment. Other studies did not report on relapse.

Because of the non-comparative nature of the studies, which were all observational, narrative descriptions reporting pooled proportions were provided rather than estimated measures of effect. The certainty of evidence was deemed to be very low for all outcomes due to very serious risk of bias, serious or very serious inconsistency within regimens, and very serious indirectness. Imprecision could not be assessed due to the lack of comparative data.

The reviewers concluded that pooled estimates need to be interpreted with caution considering the small number of studies, the potential for confounding by indication, other potential residual confounding and between-study heterogeneity regarding the assessment of neurological sequelae.

GDG considerations: While the GDG members discussed evidence of benefits of the intervention regimen and biological plausibility, they noted the very low certainty of the data. The GDG members decided to choose that the balance of effects 'does not favour either the intervention or the comparison'. This decision reflects that both the desirable and undesirable effects varied, as well as the very low certainty of the evidence overall. Recognizing how quickly the condition of children with TBM can deteriorate, GDG members were not comfortable favouring one regimen over the other, based on the very low certainty of the data.

The GDG members also noted that the feasibility of introducing the shorter intensive regimen is dependent on the setting. Acceptability, affordability and access to the component medicines (including the child-friendly ethionamide formulation, a 125 mg dispersible tablet) are important contextual factors as well as any additional implementation considerations such as the necessity and availability of monitoring tests that are needed with the shorter regimen. GDG members thought that the short intensive regimen would probably be acceptable as it includes medicines that have been in use for many years, including first line medicines and ethionamide. The intervention regimen is more costly than the comparator regimen, but refers to the costs of medicines only; GDG members stated that other costs (including to patients, families and the health system) were important.

The GDG acknowledged the limited data on alternative regimens to treat TBM and the need for continued efforts to optimize and better understand treatment options for TBM, including implementation considerations, such as dosing.

5.2.2. Subgroup considerations

Children living with HIV infection: Most studies in the review were restricted to HIV-negative children. HIV-positive children represented a small proportion of children with TBM overall, and all received the intervention regimen. In the three studies using the intervention regimen included in the evidence review, 11 children were identified as having HIV infection (of a total of 724 children). Therefore, it was not possible to undertake analyses stratified by HIV infection. An additional small study of 13 children from South Africa used an extended duration of the intervention regimen (i.e. 9 months of HRZEto). Therefore, the recommendation on the 6-month regimen does not apply to HIV-infected children who are diagnosed with TBM.

Adolescents: The population in the PICO question included both children (aged 0–9 years) and adolescents (aged 10–19 years). Based on the available information in the studies the median age of patients in the three studies using the intervention regimen were: 35 months (range: 2 months–14 years), 28 months (range: 2 months–15 years) and 30 months (5–82 months). In the studies using the comparator regimen, the age structure reported in two of the three studies was: <18 years and 3.3 years (range: 1–16 years). This recommendation therefore applies to both adolescents and children.

Other subgroup analyses: Several subgroup analyses were pre-planned by the systematic reviewers (including subgroup analyses by: age group, for patients with DR-TB (including isoniazid-resistant TB), for patients who were microbiologically confirmed versus those clinically diagnosed, by Medical Research Council stage at diagnosis, and for patients with complications including tuberculoma and hydrocephalus). However, these analyses could not be conducted due to insufficient data.

5.2.3. Implementation considerations

One key implementation consideration is the administration of the intervention regimen with the correct dosages of the included medicines, using currently available child-friendly formulations, including FDC formulations when possible. The regimen includes isoniazid, rifampicin, pyrazinamide and ethionamide, and is dosed as follows:

- Isoniazid: 20 mg per kg, maximum 400 mg daily
- Rifampicin: 20 mg per kg, maximum 600 mg daily
- Pyrazinamide: 40 mg per kg, maximum 2000 mg daily
- Ethionamide: 20 mg per kg, maximum 750 mg daily

Historically, the regimen was dosed using a child-friendly FDC (dispersible tablet) of isoniazid and rifampicin (60 mg/60 mg) with pyrazinamide and ethionamide added as single medicines. This 60/60 mg FDC has limited availability globally, while a 50/75 mg isoniazid/rifampicin dispersible tablet is widely available through the Stop TB Partnership Global Drug Facility in over 100 countries (at the time of the GDG meeting). Using this formulation, rifampicin is dosed at slightly higher mg per kg doses as the drug ratio between isoniazid and rifampicin is 1:1.5 in the formulation. Higher doses of rifampicin are being used in several other trials including the SURE trial, TBM Kids and OptiRif Kids. Results from the SURE trial and TBM Kids are expected in the coming years while the results from the OptiRif Kids trial *(74)* were published after the GDG meeting. The dosing of the shorter intensive regimen was the subject of an expert consultation convened by the WHO after the GDG meeting and information on dosing for this regimen is included in the Operational Handbook.

A dispersible paediatric formulation of ethionamide (125 mg) has been available from the Stop TB Partnership GDF since March 2018. Although orders for ethionamide are received from high MDR-TB burden countries consistently (this formulation was supplied by GDF to 41 countries between 2019 and 2021 at the time of the GDG meeting), the GDG members discussed that the paediatric formulation of ethionamide may not be available in all countries or health care levels where it is needed. Ethionamide is a component of the shorter all-oral bedaquiline-containing regimens to treat MDR/RR-TB; however, at the time that the GDG meeting was held (May-June 2021) the shorter regimen was only recommended for children aged 6 years and above.

The GDG members also noted that this regimen should ideally be used in children with TBM that is bacteriologically confirmed as drug susceptible. However, it can also be used for children who are clinically diagnosed, but there should be no suspicion of DR-TB, such as in children or adolescents who have a history of contact with a patient with confirmed DR-TB (including isoniazid resistance, rifampicin resistance or multi-drug resistance). In countries or areas with a high background prevalence of DR-TB and where ethionamide is in use to treat DR-TB, programmes and clinicians need to consider the risks and benefits of using this regimen. The current recommendation for the diagnosis of TBM is that in adults or children with signs and symptoms of TBM, Xpert MTB/RIF or Xpert Ultra should be used in cerebrospinal fluid as the initial diagnostic test rather than smear microscopy/culture (strong

recommendation, moderate certainty of evidence for test accuracy for Xpert MTB/RIF; low certainty of evidence for test accuracy for Xpert Ultra *(16)*.

5.2.4. Monitoring and evaluation

Implementation of this recommendation should be subject to ongoing monitoring and evaluation to ensure high quality implementation adapted to the local context. Uptake of the regimen and monitoring of treatment outcomes among patients who receive this regimen are also of interest. The overall incidence of TBM as a form of EPTB in children and adolescents reflects the ongoing transmission of TB to children, as well as delays in the diagnosis of TB and is therefore important information to monitor as well.

5.3. Treatment of multi-drug and rifampicin resistant TB in children

Around 25 000–32 000 children are estimated to develop MDR/RR-TB every year *(75–77)*. In 2018, 3398 children (aged below 15 years) were started on second-line treatment for MDR/RR-TB. After increasing to 5586 in 2019, due to the impact of the COVID-19 pandemic, this number dropped back to 3234 in 2020, representing only 2.5% of the total number of persons with MDR/RR-TB initiated on treatment and only 10.1%–12.9% of the estimated number of children with incident MDR/RR-TB *(78)*. Treatment outcomes reported in a systematic review and individual patient data meta-analysis conducted for the 2018 WHO DR-TB treatment guidelines, showed an overall successful treatment outcome of 78% in children treated for MDR-TB (75% of confirmed and 89% of clinically diagnosed children) *(79)*. Appropriate treatment of children with MDR/RR-TB with a WHO recommended regimen is an important step in ensuring a successful treatment outcome, as well as preventing the acquisition of further drug resistance. Other measures to prevent drug resistance or limit its spread include treatment of drug-susceptible TB with a WHO recommended regimen (to avoid misuse or overuse of antibiotics), infection prevention and control, the use of WHO recommended molecular diagnostic tests and patient support. Recommendations on each of these areas are included in this consolidated guideline and on the WHO TB KSP. The implementation and use of new molecular diagnostic tools, treatment decision algorithms and WHO recommended treatment regimens are vital components to ensure antimicrobial stewardship.

5.3.1. The use of bedaquiline in children with MDR/RR-TB aged below 6 years

Recommendation

In children with MDR/RR-TB aged below 6 years, an all-oral treatment regimen containing bedaquiline may be used *(conditional recommendation, very low certainty of the evidence)*.

Remarks

- This recommendation applies to and complements current WHO recommendations on shorter and longer regimens that contain bedaquiline *(9)*:

  – A shorter all-oral bedaquiline-containing regimen of 9–12 months duration is recommended in eligible patients with confirmed multidrug- or rifampicin-resistant tuberculosis (MDR/RR-TB) who have not been exposed to treatment with second-line TB medicines used in this regimen for more than 1 month, and in whom resistance to fluoroquinolones has been excluded. *(Conditional recommendation, very low certainty in the evidence)*

  – Bedaquiline should be included in longer multidrug-resistant TB (MDR-TB) regimens for patients aged 18 years or more. *(Strong recommendation, moderate certainty in the estimates of effect)*

  – Bedaquiline may also be included in longer MDR-TB regimens for patients aged 6–17 years. *(Conditional recommendation, very low certainty in the estimates of effect)*

Justification and evidence

PICO question: In MDR/RR-TB patients aged below 6 years, should an all-oral treatment regimen containing bedaquiline versus other regimens conforming to WHO guidelines without bedaquiline be used?

Historical context: In 2012, for the first time in over 40 years, a new TB drug with a novel mechanism of action – namely bedaquiline – was granted accelerated approval by the United States Food and Drug Administration (US-FDA) for the treatment of MDR-TB among adults (≥18 years of age) for whom an effective treatment regimen was not otherwise available *(80)*. In 2013, following an expert group meeting which reviewed available Phase IIb trial data on the efficacy and safety of bedaquiline, the WHO issued an interim policy guidance comprising a conditional recommendation and based on very low confidence in the estimates of effect, indicating that bedaquiline may be added to a WHO-recommended regimen in adults with MDR-TB (≥18 years of age) under specific conditions *(81)*.

In 2016, after the introduction and roll-out of bedaquiline in an increasing number of countries and with more data available on its use, the WHO convened a GDG meeting to re-evaluate the added benefit of bedaquiline in conjunction with a WHO-recommended longer regimen for the treatment of MDR-TB. At this time, the GDG agreed that there was not enough evidence to prompt a change in the 2013 recommendation *(82)*.

In 2019, after a GDG meeting where new evidence was reviewed from the adult IPD and two ongoing paediatric studies (TMC207-C211 and IMPAACT P1108), WHO issued the consolidated guidelines on DR-TB treatment *(83)*, where bedaquiline was recommended for inclusion in longer MDR-TB regimens for persons aged 18 years or more (strong recommendation, moderate certainty in the estimates of effect) and in longer MDR-TB regimens for children and adolescents aged 6–17 years (conditional recommendation, very low certainty in the estimates of effects). Also in 2019, following the review of available data on the programmatic implementation of a shorter, all oral treatment regimen including bedaquiline in South Africa, the WHO recommended a shorter, all-oral bedaquiline containing regimen of 9–11 months for eligible persons with confirmed MDR/RR-TB who were not exposed to treatment with second-line TB medicines used in this regimen for more than 1 month, and in whom resistance to fluoroquinolones was excluded (conditional recommendation, very low

certainty in the evidence) *(9)*. This recommendation on the shorter all-oral bedaquiline-containing regimen replaced earlier recommendations on shorter regimens which contained an injectable agent. In a new IPD meta-analysis used as evidence for the 2020 WHO guidelines, bedaquiline use resulted in significantly fewer episodes of treatment failure, relapse and death *(84)*. At the time, there was limited experience in the use of bedaquiline in children aged under 6 years, but experience of its use in adolescents, patients with EPTB disease and people living with HIV was growing. Earlier recommendations on the composition of longer regimens indicated that bedaquiline could also be included in such regimens for patients aged 6–17 years; hence, the all-oral bedaquiline-containing regimen was also conditionally recommended for use in eligible children and adolescents aged 6 years and above.

Gap: The recommendations that apply to children were based on extrapolation of efficacy data in adults, in combination with PK and safety data from phase II trials in children aged 6–17 years. However, a recommendation on the use of bedaquiline in children aged less than 6 years was not possible in the past, due to a lack of evidence, particularly on PK, safety and tolerability. The medicines that compose the shorter all-oral bedaquiline-containing regimen have been part of MDR-TB regimens for many years, in similar combinations, for both adults and children. The associated adverse drug reactions have been widely described and the drug dosages established. This however did not apply to bedaquiline at the time of the 2019 GDG on DR-TB, and the use of bedaquiline for young children in both shorter and longer regimens was therefore identified as a gap to be addressed as part of the 2021 update of the child and adolescent TB guidelines.

Evidence: To answer the PICO question on the use of bedaquiline in children under the age of 6 years, data from two phase II trials (TMC207-C211 and IMPAACT P1108) were reviewed by the GDG. TMC207-C211 is a phase II, open-label, single-arm study to evaluate the PK, safety, tolerability and anti-mycobacterial activity of bedaquiline in combination with a background regimen of MDR-TB medications for the treatment of children and adolescents 0–17 years of age who have bacteriologically confirmed or clinically diagnosed pulmonary and selected forms of extrapulmonary MDR-TB.[32] IMPAACT P1108 is a phase I/II dose finding modified age de-escalation study to evaluate the PK, safety and tolerability, of bedaquiline in combination with optimized individualized MDR-TB regimens in HIV-infected and HIV-uninfected children with clinically diagnosed or confirmed pulmonary (intra-thoracic) and selected forms of extrapulmonary MDR-TB.[33]

As data reviewed from TMC207-C211 corresponded to children aged 5–18 years and that from IMPAACT P1108 included children aged 0–6 years, the review of PK and safety data focused mainly on data from IMPAACT P1108. Although the sample size of the available interim data for review was small (N= 12), the GDG concluded that in children 0–6 years of age, cardiac safety signals were not 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 MDR/RR-TB IPD were analysed descriptively (24 231 records from all six WHO regions, the majority from India and South Africa). The search was conducted in April 2020. Just under 20 000 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 a lower adjusted odds ratio of injectable TB drug use. There was no statistically significant difference in successful treatment outcomes between children aged less than 6 years receiving an all-oral bedaquiline-based regimen versus those not receiving

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[32] Pharmacokinetic study to evaluate anti-mycobacterial activity of TMC207 in combination with background regimen (BR) of multidrug resistant tuberculosis (MDR-TB) medications for treatment of children/adolescents pulmonary MDR-TB (https://clinicaltrials.gov/ct2/show/NCT02354014, accessed 21 January 2022).

[33] P1108. A Phase I/II, open-label, single arm study to evaluate the pharmacokinetics, safety and tolerability of bedaquiline (BDQ) in combination with optimized individualized multidrug-resistant tuberculosis (MDR-TB) therapy in HIV-infected and HIV-uninfected infants, children and adolescents with MDR-TB disease (https://www.impaactnetwork.org/studies/p1108, accessed 21 January 2022).

bedaquiline (89% versus 97%, p=0.9). Residual confounding (including confounding by indication) was thought to be likely.

A child-friendly formulation of bedaquiline (20 mg scored uncoated tablet) is being used in the Janssen C211 study to dose children aged below 5 years and will also soon be used in an updated protocol of IMPAACT study P1108 (this study has used the 100 mg formulation to date in all age groups). No head-to-head studies were conducted to examine the bioequivalence of the 20 mg and the 100 mg formulation of bedaquiline. Indirect bioequivalence testing showed that both tablets have the same bioavailability and can be used interchangeably at the same total dose. Findings from the bedaquiline crush study *(85)* also showed that bioavailability of bedaquiline tablets suspended in water was the same as for tablets swallowed whole.

GDG considerations: The GDG discussed the desirable effects that were previously reported and noted that including bedaquiline in all-oral regimens for children will allow the construction of regimens that are more child- and family-friendly, with shorter durations (as shown by the IPD analysis, where bedaquiline-containing regimens were usually shorter than those not including bedaquiline). The GDG rated the desirable effects as moderate. The main concern noted by the panel was the lack of data on long-term safety and adverse events. However, the GDG noted that clinical experience with using bedaquiline in young children showed that the drug is tolerated well and often better than in the adult population. Therefore, the GDG agreed that the undesirable effects were small. Overall, the GDG determined that the balance between desirable and undesirable effects probably favours the use of bedaquiline in children aged below 6 years. The GDG highlighted that the benefits may vary depending on specific contexts and population characteristics, such as by nutritional status. The GDG also noted that the potential higher cost of bedaquiline in an MDR/RR-TB treatment regimen should be considered in the context of the benefits of shorter injectable free regimens (i.e. less travel, reduced time spent in clinics and fewer adverse events). In addition, they judged that equity might increase when bedaquiline becomes available to younger children, as its use would be acceptable to the majority of stakeholders, and that one of the main feasibility aspects would be related to the need for safety monitoring (i.e. access to ECG monitoring, as well as staff capacity for monitoring). However, the panel judged that the use of bedaquiline in young children was probably feasible to implement.

Subgroup considerations

Children living with HIV: While trial TMC207-C211 has not yet enrolled children living with HIV, the IMPAACT study P1108 study enrols HIV-infected and HIV-uninfected infants, children and adolescents with MDR-TB disease (of the nine children aged below 6 years enrolled and with PK data at the time of the GDG report, one was HIV-infected). In the paediatric IPD, 12 of the 40 children (30%) aged below 6 years treated with a bedaquiline-containing regimen were HIV positive, as compared to 364 out of 1992 (20%) treated with DR-TB regimens not including bedaquiline.

The composition of treatment regimens for MDR/RR-TB does not usually differ substantially for people living with HIV; bedaquiline may be used in all children, irrespective of HIV status. Known drug-drug interactions, such as between bedaquiline and efavirenz, need to be avoided.

Extrapulmonary TB: The shorter, all oral bedaquiline-containing regimen is contraindicated in children with extrapulmonary forms of TB other than TB lymphadenopathy (see implementation considerations for the full eligibility criteria). Children with these forms of EPTB should be treated with longer regimens, composed of medicines from groups A, B and C *(9)*. Data on the penetration of bedaquiline across the blood-brain barrier are sparse.

Implementation considerations

Eligibility for the shorter, all-oral, bedaquiline containing regimen: The removal of the age restriction for the use of bedaquiline means that children of all ages with confirmed MDR/RR-TB and without fluoroquinolone resistance may be offered the shorter, all-oral regimen with bedaquiline,

if they meet the eligibility criteria. This regimen is composed of bedaquiline (used for 6 months), in combination with levofloxacin/moxifloxacin, ethionamide, ethambutol, isoniazid (high-dose), pyrazinamide and clofazimine for four months (with the possibility of extending to 6 months if the patient remains sputum smear positive at the end of four months); followed by 5 months of treatment with levofloxacin/moxifloxacin, clofazimine, ethambutol and pyrazinamide. The eligibility criteria are:

- No extensive TB disease
- No severe EPTB (any forms other than TB lymphadenopathy)
- No resistance or suspected ineffectiveness of a medicine in the shorter regimen (except isoniazid resistance)
- No exposure to previous treatment with second-line medicines in the regimen for more than one month (unless susceptibility to these medicines is confirmed).

Extensive (or advanced) TB disease refers to the presence of bilateral cavitary disease or extensive parenchymal damage on CXR in adults. In children aged under 15 years, advanced disease is usually defined by the presence of cavities or bilateral disease on CXR. Severe EPTB refers to the presence of miliary TB or TBM (i.e. disseminated disease) *(61)*. In children aged under 15 years, extrapulmonary forms of disease other than lymphadenopathy (peripheral nodes or isolated mediastinal mass without compression) are considered as severe *(86)*. The shorter regimen should not be used in the presence of mutations in both the inhA promoter and katG on first-line LPA (MTBDRplus) in the child as this suggests that both isoniazid at high dose and thioamides are not effective *(87)*.

Promoting the use of bedaquiline in all-oral regimens for children will allow the construction of regimens that are more child- and family-friendly and shorter, which may reduce the use of second-line drugs with potentially more severe adverse events compared to bedaquiline (including, but not limited to injectables). Implementation of shorter, all-oral regimens may also facilitate the implementation of DR-TB treatment at peripheral levels of the health care system. NTPs and clinicians are therefore discouraged from using injectable agents as part of treatment regimens for MDR/RR-TB in children of all ages.

Regimen building for children not eligible for the shorter all-oral bedaquiline-containing regimen: Children who do not have bacteriological confirmation of TB and/or resistance patterns but who have a high likelihood of MDR/RR-TB (based on clinical signs and symptoms of TB, in combination with a history of contact with a patient with confirmed MDR/RR-TB) are eligible to receive bedaquiline as part of their treatment regimen. However, they do not meet the eligibility criteria for the shorter all-oral bedaquiline-containing regimen, as this regimen may only be used in people with TB with at least confirmation of rifampicin resistance in whom resistance to fluoroquinolones has been ruled out *(84)*. These children will benefit from an individualized longer treatment regimen, taking into account the drug susceptibility (and/or mutation) pattern of the most likely source case, if this information is available. Treatment duration will depend on the extent and severity of disease, as well as the response to treatment. Shortening the total treatment duration to less than 18 months may be considered in children without extensive disease *(61)*. Children with a diagnosis of rifampicin resistance only without further DST (such as a child diagnosed with Xpert MTB/RIF or Xpert Ultra testing on a stool sample but no further DST on respiratory samples) could be treated with available bedaquiline-containing regimens at the discretion of the treating clinician.

Guidance on how to construct optimal all-oral treatment regimens in children with MDR/RR-TB who are not eligible for the shorter, all-oral bedaquiline-containing regimen is provided in the operational handbook, considering their age, resistance patterns in the child or most likely source case and extent of TB disease. The construction of these treatment regimens is aligned to the *WHO consolidated guidelines on tuberculosis. Module 4: treatment – drug-resistant tuberculosis treatment*, the priority drug groupings in groups A, B and C as well as the minimum number of effective drugs required *(61)*.

Duration of bedaquiline use: Evidence assessed by a GDG in November 2019 supported the safe use of bedaquiline beyond 6 months in people with TB who received appropriate schedules

of baseline and follow-up monitoring. However, at that time the GDG was not able to assess the relative effectiveness of prolonged bedaquiline use, owing to limited evidence and potential residual confounding in the data. The regimen needs to have at least three effective agents if bedaquiline is stopped at six months; thus, if after 6 months, one of the three remaining agents needs to be stopped because of toxicity, then it needs to be replaced. The replacement medicine would be chosen from either group B (unless both clofazimine and cycloserine or terizidone are already included) or group C. The choice from group C is determined by the order in which the medicines are ranked, and the individual circumstances of the patient and setting *(9)*.

Concurrent use of bedaquiline and delamanid: The GDG held in November 2019 found insufficient evidence to allow for a statement about the effectiveness of concurrent use of both medicines. However, the group concluded that the safety data assessed in 2019 suggest no additional safety concerns with regard to the concurrent use of bedaquiline and delamanid. Therefore, bedaquiline and delamanid may be used in people with MDR/RR-TB who have limited options for other treatment, i.e. for those with an insufficient number of other effective drugs included in their regimen, such as due to an extensive drug-resistance profile or intolerance to other second-line TB medications. Appropriate schedules of safety monitoring (at baseline and throughout treatment) should be in place for these people with TB, including ECG and electrolyte monitoring, and clinicians should be cognizant of other medicines in the regimen that can either prolong the QT interval or cause other potential adverse events *(9)*.

MDR/RR-TB case detection in children: Efforts to implement child-friendly DR-TB regimens including bedaquiline should be implemented in parallel with increased efforts at the country level to close the case detection gap. Evidence-based, integrated treatment decision algorithms (see chapter 4) that are specific for different settings with varying access to diagnostic tests and CXR, apply to children with presumptive MDR/RR-TB as well, and need to be widely implemented to ensure that MDR/RR-TB is detected and effectively treated among children.

Administration of bedaquiline: Dosing guidance for the use of bedaquiline in children below 6 years of age is provided in the operational handbook, based on an expert consultation on dosing that was conducted as a follow up to the GDG meeting. The guidance takes into account the child-friendly formulation of bedaquiline that was approved by the US FDA in May 2020 and has been available from the Stop TB Partnership GDF since June 2020, namely a 20 mg scored tablet which can be taken whole or dispersed in water for patients who have difficulty swallowing intact tablets. This formulation of bedaquiline has been included in the 8th WHO Essential Medicine List for Children (EMLc), released in October 2021 *(88)*. To aid with administration, the dispersed mixture in water can be further mixed with a beverage or soft food or crushed and mixed with soft food immediately prior to its use and administered (see below for more details). It should also be noted that the findings from the bedaquiline crush study showed that bioavailability of bedaquiline tablets suspended in water was the same as for tablets swallowed whole *(85)*. Therefore, if the 20 mg formulation of bedaquiline is not available, the crushed 100 mg formulation dissolved in water can be used to dose younger children without compromising bioavailability.

Concomitant food intake is an important factor to consider when evaluating bioavailability. Bedaquiline bioavailability was optimized in the trials when co-administered with a high-fat meal. In practice, feeding frequency needs to be considered. In infants, feeding frequency is higher and favours the administration with high-fat meals, but it should also be considered that buffering capacity increases with increased feeding frequency. The paediatric bedaquiline formulation can be prepared and administered with a variety of foodstuffs (including water, milk products, apple juice, orange juice, cranberry juice, carbonated beverages, yoghurt, apple sauce, mashed banana and porridge) to improve palatability. The formulation is also stable for eight hours if the preparation is stored in a syringe. It should ideally be taken with a high-fat meal, and administration on an empty stomach should be avoided as bedaquiline drug exposures are reduced.

Clinical monitoring: The risk of emergence of bedaquiline resistance should be a key consideration when the drug is being used. Due to the difficulties in obtaining a suitable specimen from children aged below 6 years, performing DST may be challenging. However, if there are concerns about acquired drug resistance, every effort should be made to obtain a suitable sample, such as gastric aspirate, sputum induction or NPA (stool is not a suitable sample for conducting DST).

In the IMPAACT P1108 study, none of the children aged below 6 years had QT prolongation in any of the categories of 60 milliseconds and above. Almost all children also received clofazimine. Three children (of 11; 27%) experienced QT prolongation of 30–60 milliseconds, which was described as mild and insignificant. In general, the use of bedaquiline in populations with underlying cardiac conduction abnormalities and concomitant medications that prolong QTc needs to be carefully considered. A major implementation consideration includes the need for safety monitoring, as well as the need to build staff capacity (training, capacity building) to ensure that appropriate safety monitoring is put in place. Additional costs associated with wider implementation of bedaquiline (in addition to the higher cost of the drug), include availability of ECG machines, appropriate monitoring and trained staff to perform these activities. However, the GDG felt that savings related to potential shorter treatment duration as well as the avoidance of additional resource requirements related to injectable use (such as for monitoring with audiometry and implications for child development), outweigh the costs of bedaquiline introduction and implementation.

Adaptation of the recommendation to the local context will require staff capacity building and training, followed by supportive supervision and mentoring. Implementing all-oral treatment regimens will facilitate decentralization of MDR-TB treatment services and may therefore improve access to patient-centred care.

Monitoring and evaluation

People with TB, including children who receive a shorter or longer MDR-TB treatment regimen need to be monitored for response to treatment and for safety during treatment using schedules of relevant clinical and laboratory testing. This has been successfully applied in previous studies of shorter regimens under field conditions and in the programmatic setting in South Africa.

The WHO framework for active drug safety monitoring *(89)* needs to be applied to people with TB on any type of MDR-TB regimen, to ensure appropriate action and an acceptable level of monitoring for and prompt response to adverse events – alongside monitoring for treatment outcomes. Electrocardiography is indicated for children on regimens with two or three agents that are expected to prolong the QT interval. Specific biochemical tests should also be made available according to the agents included in the regimens.

In children, smear and culture monitoring of the response to treatment may be challenging, due to difficulties in obtaining appropriate specimens for testing. However, in children with a bacteriologically confirmed diagnosis, all reasonable efforts should be taken to demonstrate bacteriological conversion. Once cultures have become negative or in children who never had a confirmed diagnosis, repeated respiratory sampling may not be useful if the child is otherwise responding well clinically. Resolution of clinical symptoms and weight gain can be used as indicators of improvement. All children should have regular clinical follow-up, including weight and height monitoring. Drug dosages should be adjusted with weight gain, as needed.

Recording and reporting of details on the diagnosis, treatment regimens, clinical monitoring and treatment outcomes of children and adolescents with MDR/RR-TB is important to monitor the programmatic implementation of newly recommended regimens as well as efforts to improve case finding of children with DR-TB. Data from national programmes on the use of bedaquiline in children of all ages is important to increase the evidence base.

5.3.2. The use of delamanid in children with MDR/RR-TB aged below 3 years

Recommendation

In children with MDR/RR-TB aged below 3 years delamanid may be used as part of longer regimens *(conditional recommendation, very low certainty of evidence).*

Remarks

• This recommendation complements the current WHO recommendation on longer regimens that contain delamanid *(9)*:

– Delamanid may be included in the treatment of MDR/RR-TB patients aged 3 years or more on longer regimens *(conditional recommendation, moderate certainty in the estimates of effect).*

Justification and evidence

PICO question: In MDR/RR-TB patients aged below 3 years, should an all-oral treatment regimen containing delamanid versus other regimens conforming to WHO guidelines without delamanid be used?

Historical context In 2014, the European Medicines Agency granted a conditional marketing authorization for delamanid for the treatment of adults (≥18 years of age) with pulmonary infections due to MDR-TB when an effective treatment regimen could not otherwise be devised for reasons of resistance or tolerability *(90)*. In the same year, following a WHO convened expert group meeting that reviewed available data on efficacy and safety of delamanid, the WHO issued an interim policy guidance comprising a conditional recommendation based on very low confidence in estimates of effect, indicating that delamanid may be added to a WHO-recommended regimen in adults (≥18 years of age) with pulmonary MDR-TB *(91)*.

In 2016, given more available data on the use of delamanid in children diagnosed with MDR-TB, the WHO convened another expert panel to assess new data and develop an addendum to the 2014 interim guidance on delamanid, with specific recommendations for children with MDR-TB. Based on the assessment of this evidence and recommendations from the expert panel, the WHO recommended that delamanid may be added to the WHO-recommended longer regimen in children and adolescents (6–17 years) (conditional recommendation, very low confidence in estimates of effect) *(92)*. The WHO interim guidance on delamanid was based on data from phase I and phase II clinical trials (trials 242–12–232 and 242–12–233) and the results of other earlier studies. The use of delamanid was conditionally approved by the WHO given the limited alternative treatment options for people with MDR-TB, on the basis that the potential benefits probably outweighed the potential risks. The WHO recommendations were also conditional upon longer-term effectiveness and safety data becoming available in subsequent years, especially from phase III randomized controlled trials.

In 2016, the WHO convened a GDG meeting where the added benefit of delamanid was re-evaluated in conjunction with a WHO-recommended longer regimen for the treatment of MDR-TB but at that time, the GDG agreed that there was not enough evidence to prompt a change in the recommendation included in the interim guidance *(93)*. In 2019, after convening a GDG meeting where newly available evidence from ongoing delamanid studies was reviewed, WHO issued the consolidated guidelines on DR-TB treatment *(83)*. With respect to the use of delamanid in children younger than 6 years, the GDG judged that on the basis of findings in adults and on the pharmacological and safety data reviewed, extrapolations on efficacy should be restricted to children aged 3–5 years but not to children younger than 3 years, pending further evidence. Exposure profiles of children 3–5 years of age were comparable to adults and no higher than in children aged 6 years and older, for whom

past GDGs convened by the WHO had already recommended the use of delamanid. Additionally, based on the laboratory and cardiac data provided, no safety signals distinct from those reported in adults were observed in children aged 3–5 years. Based on this, the WHO recommended that delamanid may be included in the treatment of MDR/RR-TB for children aged 3 years or more on longer regimens (conditional recommendation, moderate certainty in the estimates of effect*); and in the priority grouping of medicines for use in longer regimens it was classified as a group C drug *(83)*. The 2019 GDG nonetheless had concerns about the feasibility of administering the correct dose to children aged 3–5 years, given that the only tablet available at the time was the one used for adults (i.e. 50 mg), which presents challenges in manipulating its contents without compromising its effectiveness. Subsequent reviews of the WHO guidelines in 2020 did not prompt any change in the 2019 recommendation, which was the one in place at the time of the GDG meeting on child and adolescent TB during May-June 2021.

Gap: The recommendations that apply to children were based on extrapolation of efficacy data in adults, in combination with PK and safety data from phase II trials for children aged 3–17 years. However, a recommendation on the use of delamanid in children aged less than 3 years has not been possible in the past, due to a lack of evidence, particularly on PK, safety and tolerability. This has made it challenging for clinicians to design all-oral regimens for children under the age of 3 years, especially for children with (or a source case with) fluoroquinolone resistance, where choices are limited among group A and B drugs. The use of delamanid in children below 3 years of age was therefore identified as a gap to be addressed as part of the 2021 update of the child and adolescent TB guidelines.

Evidence: To answer the PICO question on the use of delamanid in children under the age of 3 years, 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)[34] and from the corresponding open-label extension study (protocol 242–12–233).[35] 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 children 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 should be considered knowing that children had lower drug exposures compared to adults. However, 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 those achieved in adults.

Central nervous system effects were included in the delamanid label for both adults and children (paraesthesia, tremors, anxiety, depression and insomnia) as important potential safety concerns for the drug. In March 2021, the study sponsor released a statement of intent to modify the labelling to include hallucinations as an adverse reaction. This new safety signal has been more prevalent among children (versus adults) with 15 reports in 14 children 2–16 years of age in India, Philippines, South Africa, Tajikistan and Ukraine. Children experiencing this safety signal included some with extensively resistant forms of TB (MDR/XDR-TB) treated with delamanid under programmatic conditions (12 reports) as well as children enrolled in a clinical trial studying delamanid for TB prevention (three reports). Seven of the 15 reports were for children also receiving cycloserine (under programmatic conditions). The GDG noted the importance of side-effects involving the central nervous system in young children, considering their dynamic brain development.

In addition to data from the trials, data from a paediatric DR-TB IPD were analysed descriptively (24 231 records from all six WHO regions, the majority from India and South Africa). The search was

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[34] Pharmacokinetic and safety trial to determine the appropriate dose for pediatric patients with multidrug resistant tuberculosis (https://clinicaltrials.gov/ct2/show/NCT01856634, accessed 21 January 2022).

[35] A 6-month safety, efficacy, and pharmacokinetic (PK) trial of delamanid in pediatric participants with multidrug resistant tuberculosis (MDR-TB) (https://clinicaltrials.gov/ct2/show/NCT01859923, accessed 21 January 2022).

conducted in April 2020. Just under 20 000 of these records were used for a matched analysis of treatment outcomes in children being treated for DR-TB. The paediatric DR-TB IPD included only seven children aged below 3 years treated with delamanid, 14 children aged 3–6 years, and 69 children aged 6–12 years. All 21 children aged below 6 years were successfully treated. The number of children was insufficient for a matched analysis.

GDG considerations: The GDG noted that when the delamanid phase II trial was started, many of the companion drugs in the optimized background regimen were not widely available (such as linezolid and moxifloxacin). By the time the phase III trial started, linezolid and moxifloxacin became more accessible, which meant that the optimized background regimens in the trial were likely more effective, making it more difficult to prove the added effect of a drug (i.e. delamanid) in the intervention regimen. The GDG concluded that the desirable effects are small. The GDG discussion around the undesirable effects focused on adverse events, including those related to the central nervous system and cardiac toxicities, as well as the newly reported adverse event of hallucinations which was of some concern to GDG members given the period of dynamic brain development in children. The GDG considered that the risks and benefits (and balance of both) are very different for treating a child with resistant forms of TB (i.e. MDR/RR-TB and XDR-TB) and with limited treatment options, compared to a healthy child at future risk of developing MDR-TB (i.e. where delamanid is used for prevention). Therefore, the GDG concluded that the balance between desirable and undesirable effects probably favours the intervention. The GDG further stated that with the 25 mg dispersible tablet, that would be available in the future, the resource implications could vary. Delamanid containing longer treatment regimens were thought to potentially increase equity and be acceptable to stakeholders. In addition, the GDG judged that the use of delamanid in children of all ages would probably be feasible, especially as the child-friendly formulation of delamanid was expected to become available later in 2021 (this formulation is now available). This judgement also considered that adult tablets cannot be split, crushed or dissolved to ease administration in children without potentially altering bioavailability.

Subgroup considerations

Extrapulmonary TB: The use of delamanid in children with extrapulmonary MDR/RR-TB may be considered (as part of longer regimens used for children with extrapulmonary MDR/RR-TB) by extrapolating data from those with PTB; the delamanid trials, however, have studied PK and safety among children with pulmonary MDR/RR-TB.

Children living with HIV: Children living with HIV were not enrolled in trials 242–12–232 and 233. Although evaluated in healthy adult volunteers, reports from antiretroviral drug-drug interaction studies suggest that the CYP3A4 inhibitor lopinavir/ritonavir increases delamanid total body exposure up to 25% [GMR: 1.22 (90% CI 1.06,1.40)] (90). This increase is not clinically relevant and does not necessitate any dose adjustments. No change in delamanid exposure was observed with co-administration of either tenofovir [GMR: 0.96 (90% CI 0.84,1.10)], a CYP1A2 inhibitor, or efavirenz [GMR: 0.94 (90% CI 0.72,1.23)], a weak CYP3A4 inducer. Delamanid does not affect plasma exposure of the antiretroviral drugs tenofovir, lopinavir/ritonavir or efavirenz (94). No drug interaction studies of delamanid together with integrase inhibitors have been performed, but based on knowledge of metabolic pathways, the risk of metabolic drug interaction potential is expected to be low (95). Therefore, based on available evidence, delamanid can be given to CLHIV with MDR/RR-TB on ART regimen without dose adjustments.

Implementation considerations

Delamanid has been in use for adults and adolescents since 2014 and for children since 2016 (from 6 years of age) and 2019 (from 3 years) and therefore the implementation considerations related to its use in children below 3 years of age are an extension of those currently in place. The main implementation considerations specifically applicable to this age group are dosing based on the availability of the 25 mg dispersible formulation and the neuropsychiatric side effects.

Delamanid formulations: In the trial, delamanid was dosed with the dispersible 25 mg tablet tested in children aged 3–5 years. Bioavailability of delamanid may be altered when the 50 mg adult tablet is split, crushed or dissolved. There are also concerns that the adult tablet may shatter if attempts are made to split it, and its contents are exceedingly bitter and unpalatable. The tablets are susceptible to oxidation and heat; thus, retaining pill fragments for use at any time other than the time of administration is likely to result in the delivery of lower-than-expected active compound and unspecified oxidation by-products. The child-friendly formulation of delamanid (25 mg dispersible tablet, unscored) has been included in the 8th WHO Essential Medicine List for Children (EMLc), released in October 2021 *(88)*, was approved by the European Medicines Agency in September 2021 and has been available through the Stop TB Partnership GDF since October 2021. Children in the 0–2-year cohort in study 242–12–233 were administered a 5 mg paediatric dispersible formulation that is not expected to be commercialized. There has been no direct bioequivalence comparison for the 5 mg paediatric formulation and the 50 mg adult tablet. In a crossover bioequivalence study, neither Cmax [90%CI GMR 0.701,0.809] nor AUC [90%CI GMR 0.775,0.909] satisfied the criteria for bioequivalence as specified by regulatory agencies. As such, the 5 mg paediatric and the 50 mg adult formulations are not interchangeable *(96)*.

Dosing guidance for the use of delamanid in children below 3 years of age is provided in the operational handbook, based on an expert consultation on dosing that was conducted after the GDG meeting. The guidance takes into account the availability of the 25 mg dispersible delamanid formulation.

Administration of delamanid: Bioavailability of delamanid was optimized in the trials by administering delamanid with a high-fat meal; and therefore administration of delamanid with food is an important aspect to consider for practical implementation. In neonates, there are higher feeding frequencies, which aligns well with the goal of administering with higher-fat content.

Regimen building of longer regimens: Guidance on how to construct optimal treatment regimens for children with MDR/RR-TB (with drugs based on WHO recommended drug classification as well as optimal treatment duration) who are not eligible for shorter, all-oral regimens is provided in the operational handbook.

Duration of treatment: Shortening the total treatment duration to less than 18 months may be considered for children without extensive disease *(61)*. Extensive (or advanced) TB disease refers to the presence of bilateral cavitary disease or extensive parenchymal damage on CXR. Severe EPTB refers to the presence of miliary TB or TBM in adolescents and adults over 15 years of age. In children aged below 15 years, extrapulmonary forms of disease other than lymphadenopathy (peripheral nodes or isolated mediastinal mass without compression) are considered as severe (adapted from *(86)*).

Concurrent use of delamanid and bedaquiline, and use of delamanid beyond six months: With regards to concurrent delamanid and bedaquiline use, evidence assessed by a GDG in November 2019 included new data on concurrent bedaquiline and delamanid use. The new evidence was insufficient to allow the GDG to make a statement about the effectiveness of concurrent use of both medicines. However, the group concluded that the safety data assessed in 2019 suggest no additional safety concerns with regard to the concurrent use of bedaquiline and delamanid. Therefore, bedaquiline and delamanid may be used in people with MDR/RR-TB who have limited options for other treatment, such as those with few effective drugs that can be included in their regimen, for example due to an extensive drug-resistance profile or intolerance to other second-line TB medications. Appropriate schedules of safety monitoring (at baseline and throughout treatment) should be in place for these patients, including ECG and electrolyte monitoring, and clinicians should be aware of other medicines in the regimen that can either prolong the QT interval or cause other potential adverse events. The available evidence of delamanid use is currently limited to the on-label 6-month duration alongside other medicines in a longer regimen; prolongation beyond 6 months can be considered on a case-by-case basis *(9)*.

Monitoring and evaluation

In children, smear and culture monitoring of the response to treatment may be challenging, due to difficulties in obtaining appropriate specimens for testing, for the same reasons it is difficult to obtain a bacteriological confirmation of the diagnosis. In children with a bacteriologically confirmed diagnosis, all reasonable efforts should be taken to demonstrate bacteriological conversion. Once cultures have become negative or in children who never had a confirmed diagnosis, repeated respiratory sampling may not be useful if the child is otherwise responding well clinically. Resolution of clinical symptoms and weight gain can be used as indicators of improvement. All children should have regular clinical follow-up, including weight and height monitoring. Drug dosages should be adjusted with weight gain, as needed.

The risk of emergence of delamanid resistance should be a key consideration when the drug is being used. Due to the difficulties in obtaining a suitable sample from children aged below 3 years, performing DST may be challenging. However, if there are concerns about acquired drug resistance, every effort should be made to obtain a suitable sample, such as through gastric aspirate, sputum induction or NPA.

No cardiac safety signals distinct from those reported in adults were observed in children 0–2 years of age; however, these are largely based on subtherapeutic concentrations. Given that a QTc evaluation prior to delamanid administration may not always be feasible, it may be important to adapt risk mitigation strategies when administering delamanid in combination with other agents that prolong QTc (such as electrolytes which are stable).

Monitoring the emergence of neuropsychiatric effects (including hallucinations) in children treated with delamanid – both who are admitted to hospitals and treated in households – will be very important. Particular attention should be paid to children who are receiving other medications that have known neuropsychiatric effects, such as cycloserine. Therefore, active TB drug safety monitoring and management systems must be functional to detect, manage and report suspected or confirmed drug toxicities in a timely manner.

Recording and reporting of details on the diagnosis, treatment regimens, clinical monitoring and treatment outcomes of children and adolescents with MDR/RR-TB is important for monitoring the programmatic implementation of newly recommended regimens as well as for efforts to improve case finding of children with DR-TB. Data from national programmes on the use of delamanid in children of all ages is important to expand the evidence base.

5.4. Consolidated recommendations on TB treatment for children and adolescents

Table 6: WHO recommendations on TB treatment relevant to children and adolescents

Guidance for national tuberculosis programmes on the management of tuberculosis in children. Second edition, 2014 *(8)*
Children with pulmonary TB or tuberculous peripheral lymphadenitis who live in settings with low HIV prevalence and/or low prevalence of isoniazid resistance and children who are HIV-negative, can be treated with a three-drug regimen (HRZ) for 2 months followed by a two-drug (HR) regimen for 4 months at standard dosages.   *(Strong recommendation, moderate quality of evidence)*
Children and adolescents with severe pulmonary disease should be treated with a four-drug regimen (HRZE) for 2 months followed by a two-drug regimen (HR) for 4 months at standard dosages.   *(Strong recommendation, moderate certainty of evidence)*
Infants aged 0–3 months with suspected or confirmed pulmonary TB or tuberculous peripheral lymphadenitis should be promptly treated with the 6-month treatment regimen (2HRZ(E)/4HR). Treatment may require dose adjustment to reconcile the effect of age and possible toxicity in young infants. The decision to adjust doses should be taken by a clinician experienced in managing paediatric TB.   *(Strong recommendation, low certainty of evidence)*
Children with suspected or confirmed osteoarticular TB should be treated with a four-drug regimen (HRZE) for 2 months, followed by a two-drug regimen (HR) for 10 months, the total duration of treatment being 12 months.   *(Strong recommendation, low certainty of evidence)*
Streptomycin should not be used as part of first-line treatment regimens for children with pulmonary TB or tuberculous peripheral lymphadenitis.   *(Strong recommendation, moderate certainty of evidence)*
WHO consolidated guidelines on tuberculosis. Module 4: treatment – drug-susceptible tuberculosis treatment, 2022 update *(55)*
New patients with pulmonary TB should receive a regimen containing 6 months of rifampicin: 2HRZE/4HR.[36]   *(Strong recommendation, high certainty of evidence)*
In all patients with drug-susceptible pulmonary TB, the use of thrice-weekly dosing is not recommended in both the intensive and continuation phases of therapy, and daily dosing remains the recommended dosing frequency.   *(Conditional recommendation, very low certainty in the evidence)*
The use of FDC tablets is recommended over separate drug formulations in treatment of patients with drug-susceptible TB.   *(Conditional recommendation, low certainty in the evidence)*

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[36] This recommendation is applicable to adolescents from 15 years of age

In patients with tuberculous meningitis, an initial adjuvant corticosteroid therapy with dexamethasone or prednisolone tapered over 6–8 weeks should be used.

(Strong recommendation, moderate certainty in the evidence)

Patients aged 12 years and older with drug-susceptible pulmonary TB, may receive a 4-month regimen of isoniazid, rifapentine, moxifloxacin and pyrazinamide.

(**NEW in DS-TB guidelines**: *Conditional recommendation, moderate certainty evidence*)

WHO consolidated guidelines on tuberculosis. Module 4: treatment – drug-resistant tuberculosis treatment, 2020 update *(9)*

Regimen for rifampicin-susceptible and isoniazid-resistant tuberculosis

In patients with confirmed rifampicin-susceptible, isoniazid-resistant tuberculosis (Hr-TB), treatment with rifampicin, ethambutol, pyrazinamide and levofloxacin is recommended for a duration of 6 months.

(Conditional recommendation, very low certainty in the estimates of effect)

In patients with confirmed rifampicin-susceptible, isoniazid-resistant tuberculosis, it is not recommended to add streptomycin or other injectable agents to the treatment regimen.

(Conditional recommendation, very low certainty in the estimates of effect)

Shorter all-oral bedaquiline-containing regimen for multidrug- or rifampicin-resistant tuberculosis (MDR/RR-TB)

A shorter all-oral bedaquiline-containing regimen of 9–12 months duration is recommended in eligible patients with confirmed multidrug- or rifampicin-resistant tuberculosis (MDR/RR-TB) who have not been exposed to treatment with second-line TB medicines used in this regimen for more than 1 month, and in whom resistance to fluoroquinolones has been excluded.

(Conditional recommendation, very low certainty in the evidence in adults and adolescents)

Longer regimens for MDR- or RR-TB

In multidrug- or rifampicin-resistant tuberculosis (MDR/RR-TB) patients on longer regimens, all three Group A agents and at least one Group B agent should be included to ensure that treatment starts with at least four TB agents likely to be effective, and that at least three agents are included for the rest of treatment if bedaquiline is stopped. If only one or two Group A agents are used, both Group B agents are to be included. If the regimen cannot be composed with agents from Groups A and B alone, Group C agents are added to complete it.

(Conditional recommendation, very low certainty in the estimates of effect)

Kanamycin and capreomycin are not to be included in the treatment of MDR/RR-TB patients on longer regimens.

(Conditional recommendation, very low certainty in the estimates of effect)

Levofloxacin or moxifloxacin should be included in the treatment of MDR/RR-TB patients on longer regimens.

(Strong recommendation, moderate certainty in the estimates of effect)

Linezolid should be included in the treatment of MDR/RR-TB patients on longer regimens.

(Strong recommendation, moderate certainty in the estimates of effect)

Clofazimine and cycloserine or terizidone may be included in the treatment of MDR/RR-TB patients on longer regimens.

(Conditional recommendation, very low certainty in the estimates of effect)

Ethambutol may be included in the treatment of MDR/RR-TB patients on longer regimens.

(Conditional recommendation, very low certainty in the estimates of effect)

Pyrazinamide may be included in the treatment of MDR/RR-TB patients on longer regimens.

(Conditional recommendation, very low certainty in the estimates of effect)

Imipenem–cilastatin or meropenem may be included in the treatment of MDR/RR-TB patients on longer regimens.[37]

(Conditional recommendation, very low certainty in the estimates of effect)

Amikacin may be included in the treatment of MDR/RR-TB patients **aged 18 years or more** on longer regimens when susceptibility has been demonstrated and adequate measures to monitor for adverse reactions can be ensured. If amikacin is not available, streptomycin may replace amikacin under the same conditions.

(Conditional recommendation, very low certainty in the estimates of effect)

Ethionamide or prothionamide may be included in the treatment of MDR/RR-TB patients on longer regimens only if bedaquiline, linezolid, clofazimine or delamanid are not used, or if better options to compose a regimen are not possible.

(Conditional recommendation against use, very low certainty in the estimates of effect)

P-aminosalicylic acid may be included in the treatment of MDR/RR-TB patients on longer regimens only if bedaquiline, linezolid, clofazimine or delamanid are not used, or if better options to compose a regimen are not possible.

(Conditional recommendation against use, very low certainty in the estimates of effect)

Clavulanic acid should not be included in the treatment of MDR/RR-TB patients on longer regimens.

(Strong recommendation against use, low certainty in the estimates of effect)

The bedaquiline, pretomanid and linezolid (BPaL) regimen for multidrug-resistant tuberculosis with additional fluoroquinolone resistance

A treatment regimen lasting 6–9 months, composed of bedaquiline, pretomanid and linezolid (BPaL), may be used under operational research conditions in multidrug-resistant tuberculosis (MDR-TB) patients with TB that is resistant to fluoroquinolones, who have either had no previous exposure to bedaquiline and linezolid or have been exposed for no more than 2 weeks.

(Conditional recommendation, very low certainty in the estimates of effect)

Note: this recommendation concerns patients aged 14 years and above.

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[37] Imipenem-cilastatin and meropenem are administered with clavulanic acid, which is available only in formulations combined with amoxicillin. Amoxicillin-clavulanic acid is not counted as an additional effective TB agent, and should not be used without imipenem-cilastatin or meropenem.

Monitoring patient response to MDR-TB treatment using culture

In multidrug- or rifampicin-resistant tuberculosis (MDR/RR-TB) patients on longer regimens, the performance of sputum culture in addition to sputum smear microscopy is recommended to monitor treatment response.

(Strong recommendation, moderate certainty in the estimates of test accuracy). It is desirable for sputum culture to be repeated at monthly intervals.

Subgroup considerations: *Patients <15 years of age with MDR/RR-TB comprised less than 2% of the IPD-MA analysed for PICO question 11 (MDR/RR-TB, 2018). Younger children usually cannot produce sufficient sputum spontaneously to allow a bacteriological diagnosis (many are typically sputum smear-microscopy negative). In these patients, culture may be a more sensitive means to detect viable TB bacilli even if very few organisms are present in the sputum or other samples, below the detection threshold of direct microscopy. However, in children who are unable to expectorate, gastric aspirates or induced sputa may be possible but the repetition of such tests at monthly frequency may not be acceptable.*

6. Models of TB care for case detection and provision of TPT in children and adolescents

This chapter contains two new recommendations and other valid WHO recommendations that apply to patient support and models of care (section 6.2). The two new recommendations, on the implementation of decentralized models of care and integrated family-centred models of care to improve both case detection and the provision of TPT, are described in full detail as this information is being published for the first time. Other consolidated recommendations in this chapter are related to patient support, health education and counselling, the provision of treatment support or video supported treatment and decentralized models of care for MDR/RR-TB services.

The recommendations in this chapter have been consolidated from current WHO guidelines on TB treatment and the context in which it should be provided, namely the *Guidelines for treatment of drug-susceptible tuberculosis and patient care, 2017 update (97)* and the *WHO consolidated guidelines on tuberculosis. Module 4: treatment – drug-resistant tuberculosis treatment, 2020 update (9)*. For more information on each recommendation including the remarks, source of evidence, justification, subgroup-, implementation- and monitoring and evaluation considerations, the source guidelines or WHO TB KSP should be consulted.

Capacity for paediatric TB is often highly centralized at secondary/tertiary level, where children may present as seriously ill, after delays in accessing care. At higher levels of care, services are often managed in a vertical, non-integrated way *(10, 98)*. Health care workers at the 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 seek care *(10)*. In addition, TB screening is often not systematically part of clinical algorithms for child health, such as integrated management of childhood illness (IMCI) and integrated community case management (iCCM). Private sector providers play an increasing role as first point of care in many countries *(99)*. There are many missed opportunities for contact tracing, as well as TB prevention, detection and care due to weak integration of child and adolescent TB services with other programmes and services.

Decentralization and provision of family-centred, integrated care are highlighted as one of 10 key actions in the 2018 Roadmap *(10)*. The Roadmap highlights that consistently and systematically addressing gaps and bottlenecks along children's and adolescents' pathway through TB exposure, TB infection and TB disease can lead to reduced transmission of TB, expansion of prevention of TB infection and earlier TB diagnosis with better outcomes. Achieving this continuum of care requires collaboration across service areas, practice disciplines and sectors, community engagement, as well as decentralization and integration of service delivery at the PHC level *(10)*.

The Roadmap suggests actions to integrate child and adolescent TB into family- and community-centred care, including: (i) strengthening country-level collaboration and coordination across all health-related programmes engaged in woman, adolescent and child health – especially reproductive health, maternal, neonatal, child and adolescent health (MNCAH), nutrition, HIV, primary and community health – with clearly defined roles, responsibilities and joint accountability; (ii) decentralizing

and integrating successful models of care for TB screening, prevention and diagnosis with other existing service delivery platforms for maternal and child health (such as antenatal care (ANC), iCCM, IMCI) as well as other related services (such as HIV, nutrition, immunization); (iii) ensuring that children and adolescents with other common comorbidities (such as meningitis, malnutrition, pneumonia, chronic lung disease and HIV infection) are routinely evaluated for TB; (iv) ensuring community health strategies integrate child and adolescent TB education, screening, prevention and case finding into the training and service delivery activities; and (v) increasing awareness of and demand for child and adolescent TB services in communities and among health workers *(10)*.

This set of PICO questions examined the impact of: (i) decentralization and (ii) family-centred, integrated approaches of child and adolescent TB services on case detection in children and adolescents who present with signs and symptoms of TB. They also examine the impact of these approaches on coverage of TPT among children and adolescents.

6.1. Decentralized and family-centred, integrated models of care to deliver child and adolescent TB services

Recommendations:

In TB high burden settings, decentralized models of care may be used to deliver TB services to children and adolescents with signs and symptoms of TB and/or those exposed to TB *(conditional recommendation, very low certainty evidence)*.

Family-centred, integrated models of care to deliver TB services may be used in children and adolescents with signs and symptoms of TB and/or those exposed to TB, in addition to standard models of care *(conditional recommendation, very low certainty evidence)*.

Remarks

• These recommendations are applicable to TB services along the full cascade of care with a focus on case detection and provision of TPT.

• They are applicable to children and adolescents with signs and symptoms of TB in terms of the impact on case detection. They also apply to children and adolescents who are exposed to TB (TB contacts) who are eligible for TPT, in terms of the impact on provision of TPT. Children and adolescents with signs and symptoms who need evaluation for TB disease may also have a history of exposure to TB (TB contacts). Children and adolescents who are TB contacts who do not have signs and symptoms need to be evaluated for TPT eligibility.

• The recommendation on decentralized services refers to enhancing child and adolescent TB services at peripheral levels of the health system and closer to the community, not to replacing specialized paediatric TB services at higher levels of the health system.

• Decentralization should be prioritized for settings and populations with poor access to existing services and/or in high TB prevalence areas.

• Family-centred, integrated approaches are recommended as an additional option to standard TB services, for example alongside specialized services that may have a limited level of integration with other programmes or linkages to general health services.

• Family-centred care is a cross-cutting principle of child care at all levels of the health system.

6.1.1. Justification and evidence

PICO questions:

a. In children and adolescents with signs and symptoms of TB, should decentralization of child and adolescent TB services versus centralized child and adolescent TB services (at referral or tertiary hospital level) be used?

b. In children and adolescents exposed to TB, should decentralization of child and adolescent TB prevention and care services versus centralized prevention and care services (at referral or tertiary hospital level) be used to increase coverage of TPT in eligible children and adolescents?

c. In children and adolescents with signs and symptoms of TB, should family-centred, integrated services versus standard, non-family-centred, non-integrated services be used?

d. In children and adolescents exposed to TB, should family-centred, integrated services versus standard, non-family-centred, non-integrated services be used to increase TPT coverage in eligible children and adolescents?

For definitions of decentralization and family-centred, integrated services, please refer to the section with definitions from page xi.

Evidence: A systematic review of studies assessing the impact of decentralized, integrated or family-centred care models on TB diagnosis, treatment or prevention outcomes in children and adolescents with TB between 0 and 19 years old, comprising both children (0–9 years old) and adolescents (10–19 years old), was conducted to answer this group of PICO questions. The PubMed, Embase, Web of Science, Global Index Medicus, Global Health and Cochrane Central databases were searched in February 2021, as well as the references of 17 related reviews. 3265 abstracts from databases and 129 additional references from related reviews were identified and assessed. 516 full-text articles were assessed for eligibility, from which 25 comparative studies (7 randomized, 18 observational) were identified; one unpublished observational study was added making a total of 26 studies. Four studies (one randomized, three observational) were excluded after review because the care model described was community-based treatment support, for which a WHO recommendation already exists *(100)*. Of the remaining included studies, 16 had elements of decentralization, five had elements of integration, and three had elements of family-centred care; four studies had elements of more than one care model of interest, but were only included based on their main model, such as either decentralization or family-centred, integrated care. Most studies focused on the 0–14-year age group.

Studies where the primary intervention was decentralization mostly assessed diagnosis or case notification outcomes (n=16) *(48, 101–115)*, with fewer assessing TPT outcomes (n=3) *(106, 116, 117)*. In general, interventions that included both strengthening of diagnostic capacity in primary care settings as well as strengthening linkages between communities and facilities consistently showed an increase in case notifications and TPT initiations, while interventions that involved only community-based activities did not.

Two studies of service integration were identified *(118, 119)*, which showed limited impact on case notifications of screening in IMCI clinics or co-location of TB and ART services. The two studies of family-centred care that were identified *(120, 121)* showed that provision of socioeconomic support packages to families affected by TB was associated with increased TPT initiation and completion.

The reviewers noted that, while substantial wider literature on integration and family-centred care is available, evidence for the specific impact on child and adolescent TB outcomes is limited. Some overlap was noted between integration of TB services into non-specialized settings, such as general outpatient or primary care services, or decentralization. For the evidence review this was a slightly artificial separation, while in practice decentralization and integration into PHC may happen together.

GDG considerations: Regarding the evidence reviewed on the impact of decentralization on TB case detection, the GDG observed that two trials *(109, 111)* and one observational study of home-based screening (without facility-based strengthening) *(114)* had fewer diagnoses or notifications among children aged below 15 years in the intervention group compared to the control group, but that none of these differences were statistically significant. The GDG discussed that while there may be a reduction in case notifications at higher levels of care, TB detection may improve if children are seen by a competent clinician at the first point of access (such as at PHC level). The evidence overall was recognized as uncertain. The benefit of increased case finding and increased number of children with TB who are initiated on TB treatment was considered to outweigh the concern for overtreatment. Therefore, undesirable effects for case detection were considered trivial. The GDG discussed potential risks of provision and management of TPT at the peripheral level, including undetected drug-related adverse events such as hepatotoxicity and insufficient capacity to manage these. In addition, there may be a risk of TB disease being treated with a course of TPT rather than with a complete treatment regimen. All these undesirable events can potentially happen but were considered rare and not of major concern. Therefore, undesirable effects for TPT provision were considered trivial as well. Overall, the GDG agreed that the balance of desirable and undesirable effects probably favours decentralized TB services for case detection and provision of TPT to children and adolescents. The panel noted that differences in setting and availability of adequate resources are important considerations.

The GDG discussed that family-centred, integrated care includes interventions at the household level to identify members of the household requiring evaluation for TB disease, TPT, treatment support, etc. Some overlap between integration of TB services into non-specialized settings such as general outpatient or primary care services, and decentralization was noted. For the evidence review, this was a slightly artificial separation, while in practice decentralization and integration into PHC may happen together. Overall, despite a lack of evidence on undesirable effects and low quality of the data, the panel agreed that there is evidence of positive effects of family-centred integrated care. It was suggested that family-centred, integrated care could be an addition to the standard of care as well as to specialized services which do not have an integration component. Family-centred care in the sense of family involvement was highlighted as a core principle of child health care.

The GDG discussed that setting specific factors related to TB burden or the organization of health services may impact feasibility, acceptability and equity considerations. They also discussed that the initial health system costs to establish decentralized and family-centred, integrated services may be relatively high (such as infrastructure, human resources, training, equipment, community engagement), but that costs are likely to decrease over time, assuming that people with TB are effectively managed and TPT is provided at the peripheral level, leading to a reduction in TB incidence. Decentralized and family-centred, integrated services may result in important savings for affected families. Equity was considered an important cross-cutting issue impacting cost as well. The GDG highlighted that TPT implementation can be very challenging with high levels of loss-to-follow-up in programmes implemented at higher levels of the health system, considering that children who are eligible for TPT are not sick. The panel agreed that decentralization and integration of services can potentially increase equity and enhance the success of the programme and judged that cost-effectiveness probably favours decentralized and family-centred, integrated approaches to both case finding and provision of TPT.

While the GDG stressed the importance of taking into consideration the potential impact of stigma when decentralizing TB services for children and adolescents to lower levels, the panel judged that decentralized approaches are probably acceptable to key stakeholders. Overall decentralized and family-centred, integrated approaches were judged feasible to implement, although feasibility may vary depending on infrastructure, available funding and the structure of the NTP, among others. However, adequate investment is critical to enable the acceptability, equity and feasibility of decentralized approaches.

6.1.2. Subgroup considerations

Adolescents have a disease presentation that is similar to adults, and therefore may need different interventions than young children. Additional subgroup considerations for adolescents are included in the operational handbook, taking into account their specific health-seeking behaviour and the need for adolescent-friendly services.

TB contacts: Provision of TPT has focused mainly on children under 5 years of age for many years. In 2018, target groups for the provision of TPT were expanded to include contacts of all ages *(122)*. Available data from the global TB database *(78)* show that coverage of TPT in household contacts is poor, especially in those over 5 years of age.

In children with common illnesses with overlapping signs and symptoms of TB, approaches to integrate TB services in their care can improve case detection and provision of TPT.

These subgroups include:

- Children with SAM
- Children with severe pneumonia
- Children living with HIV
- Children with other chronic diseases.

6.1.3. Implementation considerations

Health system requirements: Training of health care workers at peripheral levels of the health system is a critical requirement to ensure adequate implementation of decentralized approaches. Similarly, resources are needed at the peripheral level, especially initially to establish services. It is expected that as services are established and effectively implemented, the long-term impact will result in a decrease in TB incidence with an associated reduction in resource requirements. A phased approach may be applied if this is most appropriate in the country or area, depending on the local burden of TB, availability of domestic or donor funding and of technical and programmatic support.

Factors to consider in decentralizing child and adolescent TB services include: existing infrastructure (such as baseline health infrastructure, needs for expansion or upgrading), applicable regulatory framework, financing, choosing between an operational research setting or programmatic implementation, human resource issues (including staffing requirements and human resources development, such as capacity building/training and consultation skills), monitoring and evaluation, conducting qualitative research into community needs, perceptions (including views on stigma) and suggestions. Decentralization of services to the PHC level requires child and adolescent TB services to be integrated within general PHC services, resulting in possible significant overlap between decentralization and family-centred, integrated approaches.

Contact investigation: Active contact investigation at community and household level is a critical intervention for enhancing both case finding and provision of TPT among children and adolescents.

Task shifting: Decentralization should not only concern the levels of the health system but should ideally also take place within the same structure, by training all health care providers of all child and adolescent care services in the recognition and management of TB. This so-called task shifting was mentioned by the GDG as an important implementation factor.

Family-centred and integrated care: Although in child health, care evolves around the family, the concept of family-centred care has not been well defined. Family-centred care is related to the more common concept of patient-centred care. In the End TB Strategy *(6)*: "Patient-centred care involves systematically assessing and addressing the needs and expectations of patients. The objective is to provide high-quality TB diagnosis and treatment to all patients – men, women and children – without their having to incur catastrophic costs. Depending on patients' needs, educational, emotional and

economic support should be provided to enable them to complete the diagnostic process and the full course of prescribed treatment." Multiple descriptions exist that include components of support and education based on individual needs, building a patient-provider partnership and participatory decision-making. Family-centred care also includes interventions at the level of the household to identify members of the household requiring evaluation for TB disease, TPT, treatment support, etc. As the concept of family-centred, integrated care may be setting specific, one of the first steps in implementation includes clarifying which definition applies to the setting in which it is to be implemented. Similarly, the implementation strategy varies by setting and needs to be country- or region-specific, informed by social, cultural and societal values.

The package of TB services to be provided needs to be defined and developed by the NTP, in close coordination with other relevant programmes, such as through an existing child and adolescent TB technical working group. This package needs to be based on identifying and addressing capacity needs for national programmes interested in the uptake of proposed interventions, and ideally based on family and community perceptions on the ideal family-centred model of care. It could include community-based models for active contact investigation, identifying children with TB signs and symptoms or exposure as part of routine growth monitoring services, or an integrated model for IMCI integration, starting with the sick child and identifying signs and symptoms pointing to a high likelihood of TB.

Integration can start within the family, by equipping the family with the knowledge to recognize signs and symptoms to understand the importance of a history of contact, to know when to seek help at the health care facility and how to minimize stigma related to TB. High yield entry points provide a good starting point within the health system. For example, child and adolescent TB services can be integrated in malnutrition clinics, ANC, the expanded programme on immunization, inpatient sites, adult TB and chest clinics, HIV and general paediatric clinics. Ideally TB care should be integrated into general health services, rather than be limited to enhanced coordination between two programmes. However, defining an optimal patient flow between services and creating strong linkages between child health entry points and TB clinics remains essential, especially in facilities where services are physically separated. This is critical to enhance the quality of services, including the follow-up of persons with TB during the diagnostic evaluation, to also ensure accuracy of recording and reporting. In the early phase, pilot programmes could be considered, which should be evaluated and adjusted as needed and then scaled up.

Factors to consider in designing an integrated approach to child and adolescent TB care include existing infrastructure (such as baseline health infrastructure, needs for expansion or upgrading), the applicable regulatory framework, financing, choosing between an operational research setting or programmatic implementation, human resource issues (including staffing requirements and human resources development such as capacity building/training and consultation skills), monitoring and evaluation, conducting qualitative research into community needs, perceptions (including views on stigma) and suggestions.

Differentiated service delivery (DSD): DSD is a person-centred approach developed in the HIV programme that simplifies and adapts HIV services across the cascade of care in ways that both serve the needs of people living with and vulnerable to HIV and optimize the available resources in health systems. The principles of DSD can be applied to prevention, testing, linkage to care, ART initiation and follow-up, and integration of HIV care and coinfections and comorbidities *(123)*. This approach embraces the idea that when families are given the choice to interact with the health system, it could provide a possible mechanism for integration of child and adolescent TB services within primary health or other programmes. Examples of implementing DSD for children and adolescents with or at risk of TB are provided in the operational handbook.

6.1.4. Monitoring and evaluation

Moving to decentralized, family-centred, integrated services requires careful planning and regular monitoring of implementation against the plan. The capacity needs of NTPs for implementing the proposed interventions need to be identified and addressed.

Enhanced data collection around child and adolescent TB potentially takes a substantial amount of additional time and detailed data collection may only be feasible in specific operational research settings. Programmes generally have registers in place for contact investigation, treatment registration and outcomes, as well as TPT registers. The use of these (preferably electronic) tools is important as programmes move to a more decentralized and family-centred, integrated approach, to ensure comprehensive management and treatment. The use of these tools needs to be evaluated and enhanced, including through operational research.

It will be important to monitor the number of children diagnosed at different levels of the health system, including the proportion of children that have bacteriological confirmation, the proportion who were clinically diagnosed as well as the number of children initiated on and completing TPT. Disaggregation of data by sex will be important to evaluate the impact on gender equity. Evaluating the quality of services (covering the quality of all steps in the patient pathway, from screening, to diagnosis and treatment) as well as client satisfaction are important components as well.

6.2. Consolidated recommendations on models of TB care relevant to children and adolescents

Table 7: WHO recommendations on models of TB care relevant to children and adolescents

WHO consolidated guidelines on tuberculosis. Module 4: treatment – care and support during tuberculosis treatment *(100)*
Health education and counselling on the disease and treatment adherence should be provided to patients on TB treatment.   *(Strong recommendation, moderate certainty in the evidence)*
A package of treatment adherence interventions[38] may be offered for patients on TB treatment in conjunction with the selection of a suitable treatment administration option.[39]   *(Conditional recommendation, low certainty in the evidence)*

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[38] Treatment adherence interventions include social support such as patient education and counselling, material support (e.g. food, financial incentive, and transport fee); psychological support; tracers such as home visit or digital health communication (e.g. SMS, telephone call); medication monitor; and staff education. The interventions should be selected on the basis of the assessment of individual patient's needs, provider's resources and conditions for implementation.

[39] Suitable treatment administration options include various forms of treatment support, such as video-supported treatment and regular community of home-based treatment support.

One or more of the following treatment adherence interventions (complementary and not mutually exclusive) may be offered to patients on TB treatment or to health care providers:

a. tracers[40] or digital medication monitor[41] *(Conditional recommendation, very low certainty in the evidence)*

b. material support to the patient[42] *(Conditional recommendation, moderate certainty in the evidence);*

c. psychological support to the patient[43] *(Conditional recommendation, low certainty in the evidence)*

d. staff education[44] *(Conditional recommendation, low certainty in the evidence).*

The following treatment administration options may be offered to patients on TB treatment:

a. Community- or home-based treatment support is recommended over health facility-based treatment support or unsupported treatment *(conditional recommendation, moderate certainty in the evidence);*

b. Treatment support administered by trained lay providers or health care workers is recommended over treatment support administered by family members or unsupported treatment *(conditional recommendation, very low certainty in the evidence)*

c. Video supported treatment (VST) can replace treatment support when the video communication technology is available and can be appropriately organized and operated by health-care providers and patients *(conditional recommendation, very low certainty in the evidence).*

Patients with multidrug-resistant TB (MDR-TB) should be treated using mainly ambulatory care rather than models of care based principally on hospitalization.

(Conditional recommendation, very low certainty evidence)

A decentralized model of care is recommended over a centralized model for patients on MDR-TB treatment.

(Conditional recommendation, very low certainty in the evidence)

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[40] Tracers refer to communication with the patient including via SMS, telephone (voice) calls, or home visit.

[41] A digital medication monitor is a device that can measure the time between openings of the pill box. The medication monitor may have audio reminders or send an SMS to remind patient to take medications, along with recording when the pill box is opened.

[42] Material support can be food or financial support such as: meals, food baskets, food supplements, food vouchers, transport subsidies, living allowance, housing incentives, or financial bonus. This support addresses indirect costs incurred by patients or their attendants in order to access health services, and possibly tries to mitigate consequences of income loss related to the disease.

[43] Psychological support can be counselling sessions or peer-group support.

[44] Staff education can be adherence education, chart or visual reminder, educational tools and desktop aids for decision-making and reminder.

7. Special situations

This chapter includes valid WHO recommendations that apply to children and adolescents in special situations such as for the management of TB in the context of HIV infection or malnutrition and optimal feeding of infants of mothers infected with TB. The recommendations have been consolidated from several current WHO guidelines on TB/HIV coinfection and nutrition, namely the *WHO policy on collaborative TB/HIV activities: guidelines for national programmes and other stakeholders (124)*, the *Consolidated guidelines on HIV prevention, testing, treatment, service delivery and monitoring: recommendations for a public health approach, July 2021 (125)*, the *Guideline: updates on the management of severe acute malnutrition in infants and children, 2013 (60)*, and the *Guideline: Nutritional care and support for patients with tuberculosis, 2013 (126)*. For more information on each recommendation including the remarks, source of evidence, justification, subgroup-, implementation- and monitoring and evaluation considerations, the source guidelines or WHO TB KSP should be consulted.

Table 8: WHO recommendations on TB/HIV coinfection and nutrition relevant to children and adolescents

WHO policy on collaborative TB/HIV activities: guidelines for national programmes and other stakeholders, 2012 *(124)*
Routine HIV testing should be offered to all patients with presumptive and diagnosed TB. *(Strong recommendation, low certainty of evidence)*

Consolidated guidelines on HIV prevention, testing, treatment, service delivery and monitoring: recommendations for a public health approach, July 2021 *(125)*
Co-trimoxazole prophylaxis for infants, children and adolescents living with HIV
Co-trimoxazole prophylaxis is recommended for infants, children and adolescents with HIV, regardless of clinical and immune conditions. Priority should be given to all children younger than 5 years old regardless of CD4 cell count or clinical stage and children with severe or advanced HIV clinical disease (WHO clinical stage 3 or 4) and/or those with CD4 cell count ≤350 cells/mm^3. *(Strong recommendation, high certainty evidence)*
In settings where malaria and/or severe bacterial infections are highly prevalent, co-trimoxazole prophylaxis should be continued until adulthood, irrespective of whether ART is provided. *(Conditional recommendation, moderate certainty evidence)*
In settings with low prevalence for both malaria and bacterial infections, cotrimoxazole prophylaxis may be discontinued for children 5 years of age and older who are clinically stable and/or virally suppressed on ART for at least six months and with a CD4 count >350 cells/mm^3. *(Strong recommendation, very low certainty evidence).*

Co-trimoxazole prophylaxis is recommended for HIV-exposed infants from 4 to 6 weeks of age and should be continued until HIV infection has been excluded by an age-appropriate HIV test to establish final diagnosis after complete cessation of breastfeeding.

(Strong recommendation, very low certainty evidence)

Routine co-trimoxazole prophylaxis should be given to all people living with HIV with TB disease regardless of CD4 cell count.

(Strong recommendation, high certainty evidence)

General recommendations on eligibility for ART

ART should be initiated for all people living with HIV regardless of WHO clinical stage and at any CD4 cell count.

- Pregnant and breastfeeding women *(strong recommendation, moderate certainty evidence)*
- Adolescents *(conditional recommendation, low certainty evidence)*
- Children living with HIV, one year old to less than 10 years old *(conditional recommendation, low certainty evidence)*
- Infants diagnosed in the first year of life *(strong recommendation, moderate certainty evidence)*

Rapid ART initiation should be offered to all people living with HIV following a confirmed HIV diagnosis and clinical assessment.

(Strong recommendation, high-certainty evidence for adults and adolescents; low certainty evidence for children).

> Rapid initiation is defined as within seven days from the day of HIV diagnosis; people with advanced HIV disease should be given priority for assessment and initiation.

ART initiation should be offered on the same day to people who are ready to start.

(Strong recommendation, high certainty evidence for adults and adolescents; low certainty evidence for children)

Timing of ART for children and adolescents with TB

ART should be started as soon as possible within 2 weeks of initiating TB treatment, regardless of CD4 count, among adolescents and children living with HIV (except when signs and symptoms of meningitis are present). *(Adolescents: strong recommendation, low- to moderate-certainty evidence; Children and infants: strong recommendation, very low certainty evidence)*

> ART should be delayed at least 4 weeks (and initiated within 8 weeks) after treatment for TB meningitis is initiated.

First-line ART regimens

Dolutegravir (DTG) in combination with a nucleoside reverse-transcriptase inhibitor (NRTI) backbone is recommended as the preferred first-line regimen for people living with HIV initiating ART

- Adolescents *(strong recommendation, moderate certainty evidence)*
- Infants and children with approved DTG dosing *(conditional recommendation, low certainty evidence)*

A raltegravir (RAL)-based regimen may be recommended as the preferred first-line regimen for neonates

(Conditional recommendation, very low certainty evidence)

Second-line ART regimens

DTG in combination with an optimized NRTI backbone may be recommended as a preferred second-line regimen for people living with HIV for whom non-DTG-based regimens are failing.

• Adolescents *(conditional recommendation, moderate certainty evidence)*

• Children with approved DTG dosing *(conditional recommendation, low certainty evidence)*

Boosted protease inhibitors in combination with an optimized NRTI backbone are recommended as a preferred second-line regimen for people living with HIV for whom DTG-based regimens are failing.

(Strong recommendation, moderate certainty evidence)

Guidelines: updates on the management of severe acute malnutrition in infants and children, 2013 *(60)*

Infants with severe acute malnutrition who are admitted for inpatient care should be given parenteral antibiotics to treat possible sepsis and appropriate treatment for other medical complications such as tuberculosis, HIV, surgical conditions or disability.

(Strong recommendation, very low certainty evidence)

Guideline: nutritional care and support for patients with tuberculosis, 2013 *(126)*

Management of severe acute malnutrition

School-age children and adolescents (5 to 19 years), and adults, including pregnant and lactating women, with TB disease and severe acute malnutrition (very low BMI-for-age) should be treated in accordance with the WHO recommendations for management of severe acute malnutrition.

(Strong recommendation, very low certainty evidence)

Children who are less than 5 years of age with TB disease and severe acute malnutrition (mid-upper arm circumference more than 115 mm or weight-for-height/length more than three z-scores below the WHO child growth standards median, or with any degree of bilateral pitting oedema) should be treated in accordance with the WHO recommendations for the management of severe acute malnutrition in children who are less than 5 years of age.

(Strong recommendation, very low certainty evidence)

Management of moderate undernutrition

School-age children and adolescents (5 to 19 years) and adults, including lactating women, with TB disease and moderate undernutrition, who fail to regain normal body mass index after 2 months' TB treatment, as well as those who are losing weight during TB treatment, should be evaluated for adherence and comorbid conditions. They should also receive nutrition assessment and counselling and if indicated be provided with locally available nutrient-rich or fortified supplementary foods as necessary to restore normal nutritional status.

(Conditional recommendation, low certainty evidence)

Children who are less than 5 years of age with TB disease and moderate undernutrition should be managed as any other children with moderate undernutrition. This includes provision of locally available nutrient-rich or fortified supplementary foods, in order to restore appropriate weight-for-height.

(Strong recommendation, very low certainty evidence)

Patients with multidrug-resistant TB and moderate undernutrition should be provided with locally available nutrient-rich or fortified supplementary foods, as necessary, to restore normal nutritional status.

(Strong recommendation, very low certainty evidence)

A daily multiple micronutrient supplement at 1× recommended nutrient intake should be provided in situations where fortified or supplementary foods should have been provided in accordance with standard management of moderate undernutrition,[45] but are unavailable.

(Conditional recommendation, very low certainty evidence)

Nutrition screening as part of contact investigation

In settings where contact tracing is implemented, household contacts of people with TB disease should have a nutrition screening and assessment as part of contact investigation. If malnutrition is identified, it should be managed according to WHO recommendations.

(Conditional recommendation, very low certainty evidence)

Remarks:

- *There is no evidence that nutritional management of acute malnutrition of patients with TB disease should be different than for those without TB.*

- *Concerns about weight loss or failure to gain weight should trigger further clinical assessment (e.g. resistance to TB drugs, poor adherence, comorbid conditions) and nutrition assessment, in order to determine the most appropriate interventions.*

- *Closer nutritional monitoring and earlier initiation of nutrition support (before the first 2 months of TB treatment are completed) should be considered if the nutritional indicator is approaching the cut-off value for a diagnosis of severe undernutrition.*

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[45] Pyridoxine supplementation is recommended along with isoniazid treatment for all pregnant (or breastfeeding) women, as well as for people with conditions such as HIV infection, alcohol dependency, malnutrition, diabetes, chronic liver disease or renal failure. Pyridoxine provision together with isoniazid treatment was not analysed for the 2013 nutrition guideline.

8. Research priorities

This chapter includes research gaps or priorities that were identified by the GDG members while considering the evidence related to each of the PICO questions. Addressing the identified research gaps has the potential to inform the development of future research questions that can improve TB prevention and care. This list of research priorities is not exhaustive; but it complements the existing research agenda outlined in *Research priorities for paediatric tuberculosis (127)* and other WHO guidelines.

TB screening (adapted from WHO consolidated guidelines on tuberculosis. Module 2: screening – systematic screening for tuberculosis disease (11))

- Studies evaluating the use of molecular WHO recommended rapid diagnostics for screening children and adolescents.
- More research and development on better screening tools and approaches for use in children and adolescents (screening approaches that target specific and distinct age ranges including infants younger than 12 months, children younger than 5 years, children up to the age of 10 years and those aged 10–19 years).
- Data to determine the frequency with which screening should be conducted among the subpopulations of children at highest risk of TB.
- Well-designed clinical trials to provide evidence on patient-important outcomes for TB screening in children.

Diagnostic approaches

The use of integrated treatment decision algorithms in children with presumptive pulmonary TB attending health care facilities

- External validation of the newly developed integrated treatment decision algorithms, including for specific subpopulations and in various settings.
- Implementation/operational research on the use and impact of the newly developed integrated treatment decision algorithms, including how to tailor them to local epidemiological settings (such as settings with differing burdens of TB, different health care settings, including settings with limited access to CXR).
- Modelling studies to determine the potential impact of treatment decision algorithms on case detection and treatment initiation.
- Qualitative studies on the feasibility and acceptability of the newly developed integrated treatment decision algorithms among relevant stakeholders in various settings.
- Diagnostic test accuracy studies and effectiveness studies of algorithms for the diagnosis of EPTB.

The use of Xpert Ultra in gastric aspirate or stool samples to diagnose pulmonary TB in children (adapted from 2021 rapid diagnostics guidelines (16) and 2018 research priorities for paediatric tuberculosis (127))

- Evaluation of the benefits and incremental yield of combining multiple specimen types. Limited data suggest that the combination of non-invasive specimens performs comparably with traditional gastric specimens or induced sputum specimens.

- Additional operational and qualitative research to determine the best approach to less invasive specimen collection in children, including: implementation studies on a method of suction for nasopharyngeal aspiration that is appropriate for low-skill or low-resource environments; research on the use of stool as a diagnostic specimen as part of treatment decision algorithms; definition of laboratory protocols that successfully balance the ease of implementation and diagnostic performance; and the impact of stool testing on patient-important outcomes.
- Identification, evaluation and validation of host and pathogen associated biomarkers in paediatric populations as potential novel tests for TB infection, TB disease, risk of disease progression and response to treatment among children, ideally requiring non-invasive samples and for use at the point of care.
- Optimization of the current microbiological reference standard by improving and harmonizing specimen collection; supporting laboratory research to improve specimen processing to optimize diagnostic yield using current assays; and improving phenotypic and genotypic drug-susceptibility testing on paediatric clinical specimens, including on stool samples.
- Qualitative research on equity, acceptability and feasibility aspects of diagnostic approaches, including specimen types and diagnostic tools.

A four-month treatment regimen for children and adolescents with non-severe drug-susceptible TB

- Stronger evidence on the feasibility of making a diagnosis of non-severe drug-susceptible TB among children and adolescents in settings with no access to diagnostic tools, in particular to CXR.
- Evaluation of societal costs, including direct and indirect costs to persons with TB, in the implementation of shorter treatment regimens for drug-susceptible TB (including, but not limited to transport costs and loss of family income).
- Automated software for CXR reading, including differentiating severe from non-severe forms of intrathoracic TB disease among children.

MDR/RR-TB treatment regimens for children

Bedaquiline

- Treatment outcomes in children with MDR/RR-TB of all ages treated with shorter and longer all-oral, bedaquiline containing regimens.
- Studies aimed at optimizing dosing of bedaquiline in children.
- Specific cost-effectiveness analyses on the use of bedaquiline in children.
- Studies exploring mechanisms of acquisition of resistance to bedaquiline and genetic markers to identify resistance (this evidence is likely to come from studies on adults with MDR/RR-TB but will have implications for children and adolescents).
- Studies exploring the optimization of the duration of bedaquiline use in children related to PK and safety.
- Studies exploring the concomitant use of bedaquiline and delamanid in children related to PK and safety.
- Qualitative research on acceptability, equity and feasibility issues.

Delamanid

- Data on long-term safety and side-effects of delamanid, especially related to neuropsychiatric safety signals.
- Studies aimed at optimizing dosing of delamanid in children (some studies are already ongoing, such as IMPAACT P2005, "A phase I/II open-label, single-arm study to evaluate the PK, safety, and tolerability of delamanid in combination with optimized multidrug background regimen for multidrug-resistant tuberculosis (MDR-TB) in HIV-infected and HIV-uninfected children with MDR-TB)".

- Specific cost-effectiveness studies on the use of delamanid in children.
- Studies exploring mechanisms of acquisition of resistance to delamanid and genetic markers to identify resistance.
- Studies exploring the optimization of the duration of delamanid use in children related to PK and safety.

Treatment of presumed or bacteriologically confirmed drug-susceptible TB meningitis in children and adolescents

- Comparative efficacy and safety data on the short intensive and standard treatment regimens.
- Dosing for the shorter intensive regimen and for alternative regimens under research, including regimens that include higher doses of medicines than are currently recommended.
- Considerations regarding equity including equitable access to medicines in the short intensive regimen.
- Cost-effectiveness of shorter regimens versus the current standard of care.
- Feasibility and acceptability of regimens for the treatment of TBM.
- Research on the sequelae of TBM (including the type and severity of sequelae and the ability to prevent or manage them) as well as objective measures of quality of life/functionality post-treatment.
- Co-administration of anti-inflammatory agents in the treatment of children and adolescents with TBM.
- Optimal regimens to treat TBM among CALHIV.

Models of TB care for children and adolescents

Decentralization of TB services for children and adolescents with signs and symptoms of TB and for children and adolescents exposed to TB

- Cost-effectiveness of decentralization/integration for case detection and provision of TPT.
- Impact of decentralization of services on health equity.
- Acceptability and feasibility of decentralized approaches to child and adolescent TB care for case detection and for TPT provision.

Family-centred, integrated services for children and adolescents with signs and symptoms of TB and for children and adolescents exposed to TB

- Detailed description of currently operating family-centred and integrated services; associated costs and cost-effectiveness.
- Implementation research on the components of these interventions; assessment of real-world implementation of these programmes.
- Feasibility and acceptability of family-centred, integrated and/or decentralized approaches to child and adolescent TB care for case detection and TPT provision in different settings, from person with TB, caregiver and provider perspectives.
- Costs and catastrophic costs.
- Cost-effectiveness evaluations of family-centred, integrated and/or decentralized approaches, considering currently available resources (some models assume that these interventions are built upon existing structures that may not be available).
- Outcomes of interest: initiation of TPT; number of additional children and adolescents diagnosed; delay, retention in care, treatment completion, clinical outcomes (such as treatment success); qualitative research related stigma, mental health outcome, school interruption, equity.
- Evaluation of outcomes of interest using randomized/non-randomized designs and qualitative design.
- Baseline needs assessment in the community, community perceptions regarding TB care and prevention for children and adolescents.
- Research on the quality of TB diagnosis in children – addressing both under-diagnosis and over-diagnosis.

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Annex 1. WHO recommendations incorporated in the guidelines on the management of TB in children and adolescents

In order of presentation:

WHO consolidated guidelines on tuberculosis. Module 2: screening – systematic screening for tuberculosis disease. Geneva: World Health Organization; 2021.

Recommendations for investigating contacts of persons with infectious tuberculosis in low- and middle-income countries. Geneva: World Health Organization; 2012.

WHO guidelines on tuberculosis infection prevention and control, 2019 update. Geneva: World Health Organization; 2019.

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Guideline: updates on the management of severe acute malnutrition in infants and children. Geneva: World Health Organization; 2013.

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Annex 2. Supplementary table

Summary of changes to recommendations as included in the second edition of the Guidance for national tuberculosis programmes on the management of tuberculosis in children, 2014

No.	Recommendation in *Guidance for national tuberculosis programmes on the management of tuberculosis in children (second edition)* 2014, and source guideline	Status[46]	Updated recommendation and source guideline
1 2	Xpert MTB/RIF should be used rather than conventional microscopy and culture as the initial diagnostic test in children suspected of having MDR TB or HIV-associated TB *(Strong recommendation, very low quality of evidence)* Source: Automated real-time nucleic acid amplification technology for rapid and simultaneous detection of tuberculosis and rifampicin resistance: Xpert MTB/RIF system for the diagnosis of pulmonary and extrapulmonary TB in adults and children. Policy Update. 2013. Xpert MTB/RIF may be used rather than conventional microscopy and culture as the initial test in all children suspected of having TB *(Conditional recommendation acknowledging resource implications, very low quality of evidence)* Source: Automated real-time nucleic acid amplification technology for rapid and simultaneous detection of tuberculosis and rifampicin resistance: Xpert MTB/RIF system for the diagnosis of pulmonary and extrapulmonary TB in adults and children. Policy Update. 2013.	Updated	In children with signs and symptoms of pulmonary TB, Xpert MTB/RIF should be used as an initial diagnostic test for TB and rifampicin-resistance detection in sputum, gastric aspirate, nasopharyngeal aspirate and stool rather than smear microscopy/culture and phenotypic DST. *(Strong recommendation, moderate certainty for accuracy in sputum; low certainty of evidence for test accuracy in gastric aspirate, nasopharyngeal aspirate and stool)* In children with signs and symptoms of pulmonary TB, Xpert Ultra should be used as the initial diagnostic test for TB and detection of rifampicin resistance in sputum, nasopharyngeal aspirate, gastric aspirate or stool, rather than smear microscopy/culture and phenotypic DST *(**NEW** Strong recommendation, moderate certainty of evidence for test accuracy in stool and gastric aspirate; low certainty of evidence for test accuracy in sputum; very low certainty of evidence for test accuracy in nasopharyngeal aspirate).* Sources: WHO consolidated guidelines on tuberculosis. Module 3: diagnosis – rapid diagnostics for tuberculosis detection, 2021 update. 2021. WHO consolidated guidelines on tuberculosis. Module 5: management of tuberculosis in children and adolescents, 2022.

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[46] Status: Removed (the recommendation has been superseded and is no longer relevant); Copied (the recommendation remains valid and is retained unchanged); Edited (There is no change in the evidence or in the intention of the recommendation, but the precise wording has been edited); Updated (a new evidence synthesis was conducted with review by the GDG with a full evidence-to-decision procedure); Developed de novo (a new topic, subgroup or intervention has been covered with a new evidence synthesis and a full evidence-to-decision procedure by the GDG)

No.	Recommendation in *Guidance for national tuberculosis programmes on the management of tuberculosis in children (second edition)* 2014, and source guideline	Status[46]	Updated recommendation and source guideline
3	Xpert MTB/RIF may be used as a replacement test for usual practice (including conventional microscopy, culture, and/or histopathology) for testing of specific non-respiratory specimens (lymph nodes and other tissues) from children suspected of having extrapulmonary TB *(Conditional recommendation, very low quality of evidence)* Source: Automated real-time nucleic acid amplification technology for rapid and simultaneous detection of tuberculosis and rifampicin resistance: Xpert MTB/RIF system for the diagnosis of pulmonary and extrapulmonary TB in adults and children. Policy Update. 2013.	Updated	In adults and children with signs and symptoms of extrapulmonary TB, Xpert MTB/RIF may be used in lymph node aspirate, lymph node biopsy, pleural fluid, peritoneal fluid, pericardial fluid, synovial fluid or urine specimens as the initial diagnostic test rather than smear microscopy/culture. *(Conditional recommendation, moderate certainty of evidence for test accuracy for pleural fluid; low certainty for lymph node aspirate, peritoneal fluid, synovial fluid, urine; very low certainty for pericardial fluid, lymph nodes biopsy)* In adults and children with signs and symptoms of extrapulmonary TB, Xpert Ultra may be used in lymph node aspirate and lymph node biopsy as the initial diagnostic test rather than smear microscopy/culture. *(Conditional recommendation, low certainty of evidence)* In adults and children with signs and symptoms of extrapulmonary TB, Xpert MTB/RIF or Xpert Ultra should be used for rifampicin-resistance detection rather than culture and phenotypic DST. *(Strong recommendation, high certainty of evidence for test accuracy for Xpert MTB/RIF; low certainty of evidence for Xpert Ultra)* In HIV-positive adults and children with signs and symptoms of disseminated TB, Xpert MTB/RIF may be used in blood, as an initial diagnostic test for disseminated TB. *(Conditional recommendation, very low certainty of evidence for test accuracy)* Source: WHO consolidated guidelines on tuberculosis. Module 3: diagnosis – rapid diagnostics for tuberculosis detection, 2021 update. 2021.

No.	Recommendation in *Guidance for national tuberculosis programmes on the management of tuberculosis in children (second edition)* 2014, and source guideline	Status[46]	Updated recommendation and source guideline
4	Xpert MTB/RIF should be used in preference to conventional microscopy and culture as the initial diagnostic test in testing cerebrospinal fluid specimens from children suspected of having TB meningitis *(Strong recommendation given the urgency of rapid diagnosis, very low quality of evidence)* Source: Automated real-time nucleic acid amplification technology for rapid and simultaneous detection of tuberculosis and rifampicin resistance: Xpert MTB/RIF system for the diagnosis of pulmonary and extrapulmonary TB in adults and children. Policy Update. 2013.	Updated	In adults and children with signs and symptoms of TB meningitis, Xpert MTB/RIF or Xpert Ultra should be used in cerebrospinal fluid (CSF) as an initial diagnostic test for TB meningitis rather than smear microscopy/culture. *(Strong recommendation: moderate certainty of evidence for test accuracy for Xpert MTB/RIF; low certainty of evidence for test accuracy for Xpert Ultra)* Source: WHO consolidated guidelines on tuberculosis. Module 3: diagnosis – rapid diagnostics for tuberculosis detection, 2021 update. 2021.
5	Interferon-gamma release assays (IGRAs) should not replace the tuberculin skin test (TST) in low- and middle-income countries for the diagnosis of TB infection in children or for the diagnostic work-up of children (irrespective of HIV status) suspected of TB disease in these settings. *(Strong recommendation, low quality of evidence)* Source: Use of tuberculosis interferon-gamma release assays (IGRAs) in low- and middle-income countries: policy statement. 2011.	Updated	Either a tuberculin skin test (TST) or interferon-gamma release assay (IGRA) can be used to test for TB infection. *(Strong recommendation, very low certainty in the estimates of effect)* Source: WHO consolidated guidelines on tuberculosis. Module 1: prevention – Tuberculosis preventive treatment. 2020.
6	Commercial serodiagnostics should not be used in children suspected of active pulmonary or extrapulmonary TB, irrespective of their HIV status *(Strong recommendation, very low quality of evidence for the use of commercial serodiagnostics)* Source: Commercial serodiagnostic tests for diagnosis of tuberculosis: policy statement. 2011.	Copied	Commercial serodiagnostics should not be used in children suspected of active pulmonary or extrapulmonary TB, irrespective of their HIV status *(Strong recommendation, very low certainty of evidence for the use of commercial serodiagnostics)* Source: Commercial serodiagnostic tests for diagnosis of tuberculosis: policy statement. 2011.

No.	Recommendation in *Guidance for national tuberculosis programmes on the management of tuberculosis in children (second edition)* 2014, and source guideline	Status[46]	Updated recommendation and source guideline
7	Routine HIV testing should be offered to all patients, including children, with presumptive and diagnosed TB *(Strong recommendation, low quality of evidence)* Source: WHO policy on collaborative TB/HIV activities, guidelines for national programmes and other stakeholders. 2012.	Copied	Routine HIV testing should be offered to all patients, with presumptive and diagnosed TB *(Strong recommendation, low certainty of evidence)* Source: WHO policy on collaborative TB/HIV activities, guidelines for national programmes and other stakeholders. 2012.
8	The following dosages of TB medicines should be used daily for the treatment of TB in children: • Isoniazid (H) 10 mg/kg (range 7–15 mg/kg); maximum dose 300 mg/day • Rifampicin (R) 15 mg/kg (range 10–20 mg/kg); maximum dose 600 mg/day • Pyrazinamide (Z) 35 mg/kg (range 30–40 mg/kg) • Ethambutol (E) 20 mg/kg (range 15–25 mg/kg) *(Strong recommendation, moderate quality of evidence)* Sources: 1. Rapid advice: treatment of tuberculosis in children. 2010. 2. Updated dosing range for isoniazid from Thee S, Seddon JA, Donald PR, Seifart HI, Werely CJ, Hesseling AC, et al. Pharmacokinetics of isoniazid, rifampin, and pyrazinamide in children younger than two years of age with tuberculosis: evidence for implementation of revised World Health Organization recommendations. Antimicrob Agents Chemother. 2011;55:5560–7.	Copied and moved to the dosing table in the operational handbook	*Drug dosing is included in a dosing table in the operational handbook on the management of TB in children and adolescents.*

No.	Recommendation in *Guidance for national tuberculosis programmes on the management of tuberculosis in children (second edition)* 2014, and source guideline	Status[46]	Updated recommendation and source guideline
9	Children with suspected or confirmed pulmonary TB or tuberculous peripheral lymphadenitis who live in settings with low HIV prevalence[47] and/or low prevalence of isoniazid resistance[48] and children who are HIV-negative, can be treated with a three-drug regimen (HRZ) for 2 months followed by a two-drug (HR) regimen for 4 months at the dosages specified in Recommendation 8 (above) *(Strong recommendation, moderate quality of evidence)* Source: Rapid advice: treatment of tuberculosis in children. 2010.	Split into two recommendations considering that the SHINE trial was a non-inferiority trial. Therefore the 6-month regimen remains an option that can be used.	In children and adolescents aged between 3 months and 16 years with non-severe TB (without suspicion or evidence of MDR/RR-TB), a 4-month treatment regimen (2HRZ(E)/2HR) should be used. *(**NEW** Strong recommendation, moderate certainty of evidence)* The use of ethambutol in the first 2 months of treatment is recommended in settings with a high prevalence of HIV,[44] or of isoniazid resistance.[45] Children with pulmonary TB or tuberculous peripheral lymphadenitis who live in settings with low HIV prevalence[44] and/or low prevalence of isoniazid resistance[45] and children who are HIV-negative, can be treated with a three-drug regimen (HRZ) for 2 months followed by a two-drug (HR) regimen for 4 months at standard dosages. *(Strong recommendation, moderate quality of evidence)* Source: WHO consolidated guidelines on tuberculosis. Module 5: management of tuberculosis in children and adolescents, 2022.
10	Children with suspected or confirmed pulmonary TB or tuberculosis peripheral lymphadenitis and/or children with extensive pulmonary disease, living in settings where the prevalence of HIV is high and/or the prevalence of isoniazid resistance is high,[44,45] should be treated with a four-drug regimen (HRZE) for 2 months followed by a two-drug regimen (HR) for 4 months at the dosages specified in Recommendation 8. *(Strong recommendation, moderate quality of evidence)* Source: Rapid advice: treatment of tuberculosis in children. 2010.	Split into 2 recommendations: Updated (as above) i. Copied and edited for children and adolescents with extensive PTB not eligible for the new 4-month regimen (removal of the reference to recommendation 8 and of wording around the prevalence of HIV infection or isoniazid resistance as this applies to both recommendations now)	Children with severe pulmonary TB disease should be treated with a four-drug regimen (HRZE) for 2 months followed by a two-drug regimen (HR) for 4 months. *(Strong recommendation, moderate quality of evidence)* Source: Rapid advice: treatment of tuberculosis in children. 2010.

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[47] Defined as countries, subnational administrative units, or selected facilities, where the HIV prevalence among adult pregnant women is ≥1% or among TB patients is ≥5% in the 2014 *Guidance for national tuberculosis programmes on the management of tuberculosis in children (second edition) (8).*

[48] WHO does not intend to establish thresholds for low, moderate or high levels of prevalence of isoniazid resistance: NTPs will establish definitions for their own countries.

No.	Recommendation in *Guidance for national tuberculosis programmes on the management of tuberculosis in children (second edition)* 2014, and source guideline	Status[46]	Updated recommendation and source guideline
11	Infants aged 0–3 months with suspected or confirmed pulmonary TB or tuberculous peripheral lymphadenitis should be promptly treated with the standard treatment regimens, as described in recommendation 9 or 10. Treatment may require dose adjustment to reconcile the effect of age and possible toxicity in young infants. The decision to adjust doses should be taken by a clinician experienced in managing paediatric TB. *(Strong recommendation, low quality of evidence)* Source: Rapid advice: treatment of tuberculosis in children. 2010.	Copied and edited slightly (reference to recommendations 9 and 10 is removed and the standard treatment regimen has been replaced with the 6-month treatment regimen)	Infants aged 0–3 months with suspected or confirmed pulmonary TB or tuberculous peripheral lymphadenitis should be promptly treated with the 6-month treatment regimen (2HRZ(E)/4HR). Treatment may require dose adjustment to reconcile the effect of age and possible toxicity in young infants. The decision to adjust doses should be taken by a clinician experienced in managing paediatric TB. *(Strong recommendation, low certainty of evidence)* Source: Rapid advice: treatment of tuberculosis in children. 2010.
12	During the continuation phase of treatment, thrice-weekly regimens can be considered for children known not to be HIV-infected and living in settings with well-established directly-observed therapy (DOT). *(Conditional recommendation, very low quality of evidence for use of intermittent treatment in children in specific settings)* Source: Rapid advice: treatment of tuberculosis in children. 2010.	Updated	In all patients with drug-susceptible pulmonary TB, the use of thrice-weekly dosing is not recommended in both the intensive and continuation phases of therapy, and daily dosing remains the recommended dosing frequency. *(Conditional recommendation, very low certainty in the evidence)[49]* Source: WHO consolidated guidelines on tuberculosis. Module 4: treatment – drug-susceptible tuberculosis treatment, 2022 update.
13	Streptomycin should not be used as part of first-line treatment regimens for children with pulmonary TB or tuberculous peripheral lymphadenitis. *(Strong recommendation, moderate quality of evidence)* Source: Rapid advice: treatment of tuberculosis in children. 2010.	Copied	Streptomycin should not be used as part of first-line treatment regimens for children with pulmonary TB or tuberculous peripheral lymphadenitis. *(Strong recommendation, moderate certainty of evidence)* Source: Rapid advice: treatment of tuberculosis in children. 2010.

[49] Twice-weekly dosing is totally not recommended. See Guidelines for treatment of tuberculosis, fourth edition. Geneva: World Health Organization; 2010 (http://www.who.int/tb/publications/2010/9789241547833/en/).

No.	Recommendation in *Guidance for national tuberculosis programmes on the management of tuberculosis in children (second edition)* 2014, and source guideline	Status[46]	Updated recommendation and source guideline
14	Children with suspected or confirmed tuberculous meningitis and children with suspected or confirmed osteoarticular TB should be treated with a four-drug regimen (HRZE) for 2 months, followed by a two-drug regimen (HR) for 10 months; the total duration of treatment being 12 months. The doses recommended for the treatment of tuberculous meningitis are the same as those described for pulmonary TB. *(Strong recommendation, low quality of evidence)* Source: Rapid advice: treatment of tuberculosis in children. 2010.	Updated and validated for the recommendation on treatment of TBM (a new regimen was recommended as an alternative to the existing regimen) Copied and edited for the recommendation on the treatment of osteoarticular TB	Children and adolescents with suspected or confirmed TB meningitis should be treated with a four-drug regimen (HRZE) for 2 months, followed by a two-drug regimen (HR) for 10 months; the total duration of treatment being 12 months. *(Strong recommendation, low certainty of evidence)* Source: Rapid advice: treatment of tuberculosis in children. 2010. In children and adolescents with microbiologically confirmed drug or in those who have clinically diagnosed and presumed drug-susceptible TB meningitis (without suspicion or evidence of MDR/RR-TB), a 6-month intensive regimen (6HRZEto) may be used as an alternative option to the 12-month regimen (2HRZE/10HR). *(**NEW** Conditional recommendation, very low certainty of the evidence)* Source: WHO consolidated guidelines on tuberculosis. Module 5: management of tuberculosis in children and adolescents, 2022. Children with suspected or confirmed osteoarticular TB should be treated with a four-drug regimen (HRZE) for 2 months, followed by a two-drug regimen (HR) for 10 months, the total duration of treatment being 12 months. *(Strong recommendation, low certainty of evidence)* Source: Rapid advice: treatment of tuberculosis in children. 2010.

No.	Recommendation in *Guidance for national tuberculosis programmes on the management of tuberculosis in children (second edition)* 2014, and source guideline	Status[46]	Updated recommendation and source guideline
15	In settings where TB is highly endemic or where there is high risk of exposure to TB, a single dose of BCG vaccine should be given to all infants. *(Recommendation strength and evidence quality have not been graded)*[50] Source: Revised BCG vaccination guidelines for infants at risk for HIV infection. Weekly Epidemiological Record. 2007;82:193–196.	Updated in WHO position paper (based on advice from the WHO Strategic Advisory Group of Experts on Immunization (SAGE))	In countries or settings with a high incidence of TB and/or leprosy, a single dose of BCG vaccine should be given to neonates at birth, or as soon as possible thereafter, for prevention of TB and leprosy disease. If it cannot be given at birth, it should be given at the earliest opportunity thereafter and should not be delayed. Any delay in vaccination may lead to opportunities for known or unknown exposure to TB- or leprosy-infected contacts. Co-administration of BCG with the hepatitis B birth dose is safe and strongly recommended. In order to avoid missed opportunities for neonatal vaccination, BCG multi-dose vials should be opened and used despite any wastage of unused vaccine. If the birth dose was missed, catch-up vaccination of unvaccinated older infants and children is recommended since evidence shows it is beneficial. Catch-up vaccination should be done at the earliest convenient encounter with the health care system to minimize known or unknown exposure to TB or leprosy infected contacts. Countries with a low incidence of TB or leprosy may choose to selectively vaccinate neonates in recognized risk groups for developing disease. High-risk groups to be considered for vaccination include the following: • Neonates to parents (or other close contacts/relatives) with previous TB or leprosy • Neonates in households with contacts to countries with high incidence of TB and/or leprosy • Neonates in any other locally identified risk group for TB and/or leprosy

[50]   The Global Advisory Committee on Vaccine Safety (GACVS) does not use the GRADE methodology for evaluating the quality of evidence; the BCG-related recommendations will therefore remain ungraded.

No.	Recommendation in *Guidance for national tuberculosis programmes on the management of tuberculosis in children (second edition)* 2014, and source guideline	Status[46]	Updated recommendation and source guideline
			In a few countries with low TB incidence, BCG vaccination is largely replaced by intensified case detection, contact tracing and supervised early treatment.
			Studies show minimal or no evidence of any additional benefit of repeat BCG vaccination against TB or leprosy. Therefore, revaccination is not recommended even if the TST reaction or result of an IGRA is negative. The absence of a BCG scar after vaccination is not indicative of a lack of protection and is not an indication for revaccination.
			Source: BCG vaccines: WHO position paper – February 2018. Weekly Epidemiological Record. 2018;93(8):73–96.
16	In children who are known to be HIV-infected, BCG vaccine should not be given. *(Recommendation strength and evidence quality have not been graded)*[4] Source: Revised BCG vaccination guidelines for infants at risk for HIV infection. Weekly Epidemiological Record. 2007;82:193–196.	Updated in WHO position paper (based on advice from the WHO SAGE)	Children who are HIV-infected when vaccinated with BCG at birth are at increased risk of developing disseminated BCG disease. However, if HIV-infected individuals including children, are receiving ART, are clinically well and immunologically stable (CD4% >25% for children aged <5 years or CD4 count ≥200 if aged >5 years) they should be vaccinated with BCG. • In general, populations with high prevalence of HIV infection also have the greatest burden of TB; in such populations the benefits of potentially preventing severe TB through vaccination at birth are outweighed by the risks associated with the use of BCG vaccine. Therefore, it is recommended that in such populations: • Neonates born to women of unknown HIV status should be vaccinated as the benefits of BCG vaccination outweigh the risks. • Neonates of unknown HIV status born to HIV-infected women should be vaccinated if they have no clinical evidence suggestive of HIV infection, regardless of whether the mother is receiving ART.

No.	Recommendation in *Guidance for national tuberculosis programmes on the management of tuberculosis in children (second edition)* 2014, and source guideline	Status[46]	Updated recommendation and source guideline
			Although evidence is limited, for neonates with HIV infection confirmed by early virological testing, BCG vaccination should be delayed until ART has been started and the infant confirmed to be clinically and immunologically stable (CD4% >25%). Source: BCG vaccines: WHO position paper – February 2018. Weekly Epidemiological Record. 2018;93(8):73–96.
17	In infants whose HIV status is unknown and who are born to HIV-positive mothers and who lack symptoms suggestive of HIV, BCG vaccine should be given after considering local factors *(Recommendation strength and evidence quality have not been graded)* [4] Source: Revised BCG vaccination guidelines for infants at risk for HIV infection. Weekly Epidemiological Record. 2007;82:193–196.	Updated in WHO position paper (based on advice from the WHO SAGE)	Children who are HIV-infected when vaccinated with BCG at birth are at increased risk of developing disseminated BCG disease. However, if HIV-infected individuals, including children, are receiving ART, are clinically well and immunologically stable (CD4% >25% for children aged <5 years or CD4 count ≥200 if aged >5 years) they should be vaccinated with BCG. • In general, populations with high prevalence of HIV infection also have the greatest burden of TB; in such populations the benefits of potentially preventing severe TB through vaccination at birth are outweighed by the risks associated with the use of BCG vaccine. Therefore, it is recommended that in such populations: – Neonates born to women of unknown HIV status should be vaccinated as the benefits of BCG vaccination outweigh the risks. – Neonates of unknown HIV status born to HIV-infected women should be vaccinated if they have no clinical evidence suggestive of HIV infection, regardless of whether the mother is receiving ART. – Although evidence is limited, for neonates with HIV infection confirmed by early virological testing, BCG vaccination should be delayed until ART has been started and the infant confirmed to be clinically and immunologically stable (CD4% >25%). Source: BCG vaccines: WHO position paper – February 2018. Weekly Epidemiological Record. 2018;93(8):73–96.

No.	Recommendation in *Guidance for national tuberculosis programmes on the management of tuberculosis in children (second edition)* 2014, and source guideline	Status[46]	Updated recommendation and source guideline
18	Clinical evaluation of household and close contacts for TB disease should be done on the basis of their risk for having or developing TB disease or for the potential consequences of the disease if it develops. Priority should be given to contacts who are: • children with symptoms suggestive of TB; • children <5 years of age; • children with known or suspected immunocompromising conditions (especially those living with HIV); and • child contacts of index cases with multidrug-resistant or extensively drug-resistant TB (proven or suspected). *(Strong recommendation, very low quality of evidence)* Source: Recommendations for investigating contacts of persons with infectious tuberculosis in low- and middle-income countries. 2012.	Removed	
19	It is recommended that contact investigation be conducted for household and close contacts when the index case has any of the following characteristics: • has sputum smear-positive pulmonary TB; • has multidrug-resistant or extensively drug-resistant TB (proven or suspected); • is a person living with HIV; or • is a child <5 years of age. *(Strong recommendation, very low quality of evidence)* Source: Recommendations for investigating contacts of persons with infectious tuberculosis in low- and middle-income countries. 2012.	Removed	

No.	Recommendation in *Guidance for national tuberculosis programmes on the management of tuberculosis in children (second edition)* 2014, and source guideline	Status[46]	Updated recommendation and source guideline
20	Contact investigation may be conducted for household and close contacts of all other index cases with pulmonary TB, in addition to the index cases covered in Recommendation 19. *(Conditional recommendation, very low quality of evidence)* Source: Recommendations for investigating contacts of persons with infectious tuberculosis in low- and middle-income countries. 2012.	Removed	
21	Children <5 years of age who are household or close contacts of people with TB and who, after an appropriate clinical evaluation, are found not to have TB disease should be given 6 months of IPT (10 mg/kg per day, range 7–15 mg/kg, maximum dose 300 mg/day). *(Strong recommendation, high quality of evidence)* Source: Recommendations for investigating contacts of persons with infectious tuberculosis in low- and middle-income countries. 2012.	Updated	Children aged <5 years who are household contacts of people with bacteriologically confirmed pulmonary TB and who are found not to have TB disease on an appropriate clinical evaluation or according to national guidelines should be given TB preventive treatment even if TB infection testing is unavailable. *(Strong recommendation, high certainty in the estimates of effect)* Children aged ≥5 years, adolescents and adults who are household contacts of people with bacteriologically confirmed pulmonary TB who are found not to have TB disease by an appropriate clinical evaluation or according to national guidelines may be given TB preventive treatment. *(Conditional recommendation, low certainty in the estimates of effect)* The following options are recommended for the treatment of TB infection regardless of HIV status: 6 or 9 months of daily isoniazid, or a 3-month regimen of weekly rifapentine plus isoniazid,[51] or a 3-month regimen of daily isoniazid plus rifampicin. *(Strong recommendation, moderate to high certainty in the estimates of effect).*

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[51] In ages two years and above.

No.	Recommendation in *Guidance for national tuberculosis programmes on the management of tuberculosis in children (second edition)* 2014, and source guideline	Status[46]	Updated recommendation and source guideline
			A 1-month regimen of daily rifapentine plus isoniazid[52] or 4 months of daily rifampicin alone may also be offered as alternatives.
			(Conditional recommendation, low-to-moderate certainty in the estimates of effect)
			In settings with high TB transmission, adults and adolescents living with HIV who have an unknown or a positive TB infection test and are unlikely to have TB disease should receive at least 36 months of daily isoniazid preventive therapy (IPT). Daily IPT for 36 months should be given whether or not the person is on ART, and irrespective of the degree of immunosuppression, history of previous TB treatment and pregnancy in settings considered to have a high TB transmission as defined by national authorities.
			(Conditional recommendation, low certainty in the estimates of effect)
			Source: WHO consolidated guidelines on tuberculosis: Module 1: prevention – Tuberculosis preventive treatment. 2020.
22	In settings of high HIV prevalence, all household and close contacts of people with TB should be counselled and tested for HIV. *(Strong recommendation, very low quality of evidence)* Source: Recommendations for investigating contacts of persons with infectious tuberculosis in low- and middle-income countries. 2012.	Copied	In settings of high HIV prevalence, all household and close contacts of people with TB should be counselled and tested for HIV. *(Strong recommendation, very low quality of evidence)* Source: Recommendations for investigating contacts of persons with infectious tuberculosis in low- and middle-income countries. 2012.

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[52] In ages 13 and above.

No.	Recommendation in *Guidance for national tuberculosis programmes on the management of tuberculosis in children (second edition)* 2014, and source guideline	Status[46]	Updated recommendation and source guideline
23	In settings of low HIV prevalence, all household members and close contacts of people with TB who have symptoms compatible with TB disease may be offered counselling and testing for HIV as part of their clinical evaluation. *(Conditional recommendation, very low quality of evidence)* Source: Recommendations for investigating contacts of persons with infectious tuberculosis in low- and middle-income countries. 2012.	Copied	In settings of low HIV prevalence, all household members and close contacts of people with TB who have symptoms compatible with TB disease may be offered counselling and testing for HIV as part of their clinical evaluation. *(Conditional recommendation, very low quality of evidence)* Source: Recommendations for investigating contacts of persons with infectious tuberculosis in low- and middle-income countries. 2012.
24	All household contacts of an index case who is a person living with HIV should be counselled and tested for HIV. *(Strong recommendation, very low quality of evidence)* Source: Recommendations for investigating contacts of persons with infectious tuberculosis in low- and middle-income countries. 2012.	Copied	All household contacts of an index case who is a person living with HIV should be counselled and tested for HIV. *(Strong recommendation, very low quality of evidence)* Source: Recommendations for investigating contacts of persons with infectious tuberculosis in low- and middle-income countries. 2012.

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No.	Recommendation in *Guidance for national tuberculosis programmes on the management of tuberculosis in children (second edition)* 2014, and source guideline	Status[46]	Updated recommendation and source guideline
25	Children living with HIV who are more than 12 months of age and who are unlikely to have TB disease on symptom-based screening and who have no contact with a TB case: • should be offered 6 months of IPT (10 mg/kg per day, range 7–15 mg/kg, maximum dose 300 mg/day) as part of a comprehensive package of HIV prevention and care services if living in settings with a high TB prevalence (Strong recommendation, low quality of evidence) • might be offered 6 months of IPT (10 mg/kg per day, range 7–15 mg/kg, maximum dose 300 mg/day) as part of a comprehensive package of HIV prevention and care services if living in settings with a medium or low TB prevalence. (Conditional recommendation, low quality of evidence) Source: Guidelines for intensified case-finding for tuberculosis and isoniazid preventive therapy for people living with HIV in resource-constrained settings. 2011. This recommendation had been updated from the 2011 Guidelines for intensified case-finding for tuberculosis and isoniazid preventive therapy for people living with HIV in resource-constrained settings on the basis of more recent evidence.	Updated	Adults and adolescents living with HIV who are unlikely to have TB disease should receive TB preventive treatment as part of a comprehensive package of HIV care. Treatment should also be given to those on antiretroviral treatment, to pregnant women and to those who have previously been treated for TB, irrespective of the degree of immunosuppression and even if TB infection testing is unavailable. *(Strong recommendation, high certainty in the estimates of effect)* Infants aged <12 months living with HIV who are in contact with a person with TB and unlikely to have TB disease on an appropriate clinical evaluation or according to national guidelines should receive TB preventive treatment. *(Strong recommendation, moderate certainty in the estimates of effect)* Children aged ≥12 months living with HIV who are considered unlikely to have TB disease on an appropriate clinical evaluation or according to national guidelines should be offered TB preventive treatment as part of a comprehensive package of HIV prevention and care if they live in a setting with high TB transmission, regardless of contact with TB. *(Strong recommendation, low certainty in the estimates of effect)* All children living with HIV who have successfully completed treatment for TB disease may receive TB preventive treatment. *(Conditional recommendation, low certainty in the estimates of effect)* Source: WHO consolidated guidelines on tuberculosis. Module 1: prevention – tuberculosis preventive treatment. 2020.

No.	Recommendation in *Guidance for national tuberculosis programmes on the management of tuberculosis in children (second edition)* 2014, and source guideline	Status[46]	Updated recommendation and source guideline
26	Children with suspected or confirmed pulmonary TB or tuberculous peripheral lymphadenitis living in settings with a high HIV prevalence (or with confirmed HIV infection) should not be treated with intermittent regimens (that is, twice-weekly or thrice-weekly doses). *(Strong recommendation, low-to- moderate quality evidence against the use of intermittent treatment in children)* Source: Rapid advice: treatment of tuberculosis in children. 2010.	Updated	In all patients with drug-susceptible pulmonary TB, the use of thrice-weekly dosing is not recommended in both the intensive and continuation phases of therapy, and daily dosing remains the recommended dosing frequency *(Conditional recommendation, very low certainty in the evidence)* Source: WHO consolidated guidelines on tuberculosis. Module 4: treatment – drug-susceptible tuberculosis treatment, 2022 update.
27	Children with proven or suspected pulmonary TB or tuberculous meningitis caused by multidrug-resistant bacilli can be treated with a fluoroquinolone in the context of a well-functioning MDR-TB control programme and within an appropriate MDR-TB regimen. The decision to treat should be taken by a clinician experienced in managing paediatric TB. *(Strong recommendation, very low quality evidence)* Source: Rapid advice: treatment of tuberculosis in children. 2010.	Updated	In children with MDR/RR-TB aged below 6 years, an all-oral treatment regimen containing bedaquiline may be used. *(NEW Conditional recommendation, very low certainty of the evidence).* This recommendation applies to and complements current WHO recommendations on shorter and longer regimens that contain bedaquiline: • A shorter all-oral bedaquiline-containing regimen of 9–12 months duration is recommended in eligible patients with confirmed multidrug- or rifampicin-resistant tuberculosis (MDR/RR-TB) who have not been exposed to treatment with second-line TB medicines used in this regimen for more than 1 month, and in whom resistance to fluoroquinolones has been excluded. *(Conditional recommendation, very low certainty in the evidence)* • Bedaquiline should be included in longer multidrug-resistant TB (MDR-TB) regimens for patients aged 18 years or more. *(Strong recommendation, moderate certainty in the estimates of effect)*

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No.	Recommendation in *Guidance for national tuberculosis programmes on the management of tuberculosis in children (second edition)* 2014, and source guideline	Status[46]	Updated recommendation and source guideline
			• Bedaquiline may also be included in longer MDR-TB regimens for patients aged 6–17 years.
			(Conditional recommendation, very low certainty in the estimates of effect)
			In children with MDR/RR-TB aged below 3 years delamanid may be used as part of longer regimens.
			(NEW Conditional recommendation, very low certainty of the evidence).
			This recommendation complements the current WHO recommendation on longer regimens that contain delamanid:
			• Delamanid may be included in the treatment of MDR/RR-TB patients aged 3 years or more on longer regimens. *(Conditional recommendation, moderate certainty in the estimates of effect)*
			Source: WHO consolidated guidelines on tuberculosis. Module 5: management of tuberculosis in children and adolescents, 2022.
			In multidrug- or rifampicin-resistant tuberculosis (MDR/RR-TB) patients on longer regimens, all three Group A agents and at least one Group B agent should be included to ensure that treatment starts with at least four TB agents likely to be effective, and that at least three agents are included for the rest of treatment if bedaquiline is stopped. If only one or two Group A agents are used, both Group B agents are to be included. If the regimen cannot be composed with agents from Groups A and B alone, Group C agents are added to complete it.
			(Conditional recommendation, very low certainty in the estimates of effect)
			For details on drug grouping and recommendations on individual drugs to use in longer regimens, refer to the source document below.
			Source: WHO consolidated guidelines on tuberculosis. Module 4: treatment – drug-resistant tuberculosis treatment. 2020.

No.	Recommendation in *Guidance for national tuberculosis programmes on the management of tuberculosis in children (second edition)* 2014, and source guideline	Status[46]	Updated recommendation and source guideline
28	All children treated for TB should be recorded and reported by the NTP in one of two age bands (0–4 years and 5–14 years) (This recommendation is not graded: it is based on good clinical practice) Sources: Guidance for national tuberculosis programmes on the management of tuberculosis in children. 2006. Definitions and reporting framework for tuberculosis – 2013 revision. 2013.	Copied and moved to the operational handbook	This is a good practice statement and will be incorporated into the operational handbook, with revised age bands for reporting. The age bands for reporting TB in children and adolescents have been updated and are now: 0–4, 5–9, 10–14 and 15–19 years.
-	New interim recommendation	Developed de novo	In children with presumptive pulmonary TB attending health care facilities, integrated treatment decision algorithms may be used to diagnose pulmonary TB. (*NEW Interim conditional recommendation, very low certainty evidence*) Source: WHO consolidated guidelines on tuberculosis. Module 5: management of tuberculosis in children and adolescents, 2022.
-	New recommendation	Developed de novo	In TB high burden settings, decentralized TB services may be used in children and adolescents with signs and symptoms of TB and/or those exposed to TB. (*NEW Conditional recommendation, very low certainty evidence*) Family-centred, integrated services in addition to standard TB services may be used in children and adolescents with signs and symptoms of TB and/or those exposed to TB. (*NEW Conditional recommendation, very low certainty evidence*) Source: WHO consolidated guidelines on tuberculosis. Module 5: management of tuberculosis in children and adolescents, 2022.

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