

Multidrug-resistant tuberculosis in children and adolescents in the WHO European Region

Expert opinion



Abstract

Evidence-based guidance on how to manage children and adolescents infected with or having active multidrug-resistant tuberculosis (MDR-TB) is needed. The aim of this publication is to guide Member States in the WHO European Region to adequately address child and adolescent MDR-TB at the highest quality. All measures should be integrated into the Member States' respective national TB programmes and other health services managing children with MDR-TB or at risk thereof to meet the End TB Strategy goals, as well as the related objectives laid out in the Tuberculosis Action Plan for the WHO European Region 2016–2020. This publication is intended to update readers on recent scientific evidence as well as region-specific clinical and public health recommendations on child and adolescent MDR-TB. An overview of the epidemiology in the Region as well as specific aspects of managing paediatric MDR-TB is provided. Resources for national TB programme managers or clinicians are described to encourage them to seek expert advice for difficult-to-treat cases.

Keywords

WHO EUROPEAN REGION, CHILDREN AND ADOLESCENTS, TUBERCULOSIS, MULTIDRUG RESISTANCE, MDR-TB, MDR-TB INFECTION, MDR-TB TREATMENT

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Abbreviations

ART	antiretroviral therapy
BCG	Bacillus Calmette–Guérin
DR-TB	drug-resistant tuberculosis
DST	drug susceptibility testing
ECDC	European Centre for Disease Prevention and Control
IGRA	interferon- γ release assay
LTBI	latent tuberculosis infection
MDR	multidrug-resistance
MDR-TB	multidrug-resistant tuberculosis
NGS	next generation sequencing
PCR	polymerase chain reaction
TB	tuberculosis
TST	tuberculin skin test
WGS	whole genome sequencing
XDR-TB	extensively drug-resistant tuberculosis

Summary

Historically, children and adolescents have not been a priority for national programmes for tuberculosis (TB) prevention and care in the WHO European Region. Owing to the low incidence in the Region and the non-specific clinical symptoms of TB infection and disease, children with TB or at risk thereof do not routinely enter health systems through classical TB programmes. Children and adolescents were often thought to play only a minor role in transmission of TB, and as a result TB prevention and care was focussed on adults. However, children and adolescents are significantly affected by the epidemic of multidrug-resistant TB (MDR-TB) as the Region carries 25% of the global MDR-TB burden. The estimated number of children with MDR-TB in the Region was 2120 in 2016, 16% of the total incident cases, and an estimated 14.1% of latently infected children carry MDR-TB organisms. Evidence-based guidance on how to manage children and adolescents infected with or having active MDR-TB is needed.

The aim of this publication is to guide Member States in the WHO European Region to adequately address child and adolescent MDR-TB at the highest level and quality. It intends to update readers on recent scientific evidence, as well as providing region-specific clinical and public health recommendations on child and adolescent MDR-TB. Resources are provided for national TB programme managers and clinicians to encourage all involved in TB prevention and care to seek expert advice for difficult-to-treat cases from their colleagues in the Region. The specific aspects of MDR-TB in children and adolescents in the Region are also discussed. Most countries of the Region have a low incidence of childhood TB but carry a large burden of MDR-TB cases. Health-care providers involved in child health should be sensitized to TB and its clinical presentation. The region-wide epidemiology of MDR-TB among children and adolescents is summarized and it is underlined that accurate reporting and notification of child and adolescent TB cases is key to successful control of the disease. An overview of the key guideline documents currently published by WHO is given, with a particular focus on how they relate to the regional response to child and adolescent TB. The latest evidence-based and WHO recommendations on diagnosis and treatment of MDR-TB are provided, together with a summary on WHO's position on TB vaccination.

There is still a need to develop national TB guidance documents dedicated to child and adolescent TB in some Member States of the Region. All measures should be integrated into the Member States' respective national TB programmes and other health services managing children with MDR-TB or at risk thereof to meet the End TB Strategy goals as well as the related objectives laid out in the Tuberculosis Action Plan for the WHO European Region 2016–2020.

1. Background

It is estimated that, globally, 1 million children (under 15 years) develop tuberculosis (TB) each year, with 233 000 dying annually (1,2). An additional half a million cases of TB are estimated to occur each year in older adolescents (15–20 years) (2). The emergence of drug-resistant TB (DR-TB), which poses a major threat to global TB prevention and care, also affects children and adolescents. It was estimated that in 2010, globally, 32 000 children (under 15 years) developed multidrug-resistant TB (MDR-TB) (disease caused by *M. tuberculosis* resistant to isoniazid and rifampicin) (3). The large majority of MDR-TB cases (over 95%) among children are not diagnosed (4). It is often considered that MDR-TB rates in children and adolescents reflect the overall MDR-TB rates in the community, but the true burden is unknown. In young children (under 5 years), bacteriological confirmation (including of drug resistance) can be challenging and the diagnosis is commonly made clinically while taking into account the resistance pattern of the source case. While bacteriological confirmation is more readily obtained in adolescents (10–20 years) with TB, adolescents have particular challenges with access to diagnosis and care. Drug resistance in children is mostly due to primary transmission, rather than previous exposure to treatment, such as transmission of a resistant organism from household adult contacts (5,6).

In recent years, the attention being given to the challenges of TB in children and adolescents has been increasing within the global public health and TB prevention and care agendas (7). Historically, these groups were not a priority for national programmes for TB prevention and care, which focused on the identification and treatment of the most infectious cases (8,9). Yet, children and adolescents in countries of the WHO European Region are significantly affected by the MDR-TB epidemic, as the Region carries 25% of the global MDR-TB burden (1). Among the 53 Member States of the European Region, 9 countries are included in the world's 30 high MDR-TB burden states. These nine countries are all geographically located in the eastern part of the Region (10). In 2010, a representative survey conducted in Minsk, Belarus, showed alarming levels of drug resistance with nearly 50% of TB cases classified as MDR-TB (11).

DR-TB in the Region is difficult to treat, and treatment success among people diagnosed with MDR-TB remains low, with less than 50% of cases treated successfully. While this is similar to the low rates of treatment success for MDR-TB that are reported globally (1), much higher treatment success rates for MDR-TB in children and adolescents can be achieved and have been reported, reaching up to 90% under optimal conditions (12,13).

The mandate of the WHO Regional Office for Europe, with regards to its TB activities, is set out in the Consolidated Action Plan to Prevent and Combat Multidrug- and Extensively Drug-resistant Tuberculosis in the WHO European Region 2011–2015 (14) and the follow-up document, the

Tuberculosis Action Plan for the WHO European Region 2016–2020 (15). The latter states that, among the activities related to areas of intervention, Member States ought to keep their paediatric TB guidelines up to date, ensure universal access to treatment and uninterrupted drug supply, and sustain countrywide supply and use of first-line fixed-dose combination drugs for paediatric patients (15). The Regional Office has further set out its goals in the Roadmap to Implement the Tuberculosis Action Plan for the WHO European Region 2016–2020(10).

One of the key pillars of TB prevention and care, as recommended by WHO, is contact tracing. This activity may identify cases of TB disease as well as individuals with TB infection who may develop disease in the future. Treating individuals with TB disease will prevent further transmission and treating those with TB infection will prevent future disease (16). One indicator mentioned in the 2016–2020 roadmap, and consistent with targets set by the Stop TB Partnership’s Global Plan to End TB 2016–2020 (17), is 90% treatment coverage of TB infection in child contacts under 5 years of age, defined as the number of children aged under 5 years that are started on TB infection treatment who are household contacts of TB cases, divided by the number of all child contacts under 5 years old eligible for treatment of TB infection (10). The target of 90% was met only by Azerbaijan, while the regional average for this indicator was 75.3%, based on data from 12 countries that reported these data to WHO (18).

In its 2010 Special Report, *Progressing towards TB elimination*, the European Centre for Disease Prevention and Control (ECDC) proposed using the trend in the ratio of case notification rates in children to case notification rates in adults as a progress indicator, since the case notification rate of TB in children, notably infants, is an indirect measure of the level of transmission in the community (19). This illustrates the importance of contact tracing and TB infection treatment among children, since a higher rate of primary progression to TB is observed in this population. Thus, a lower transmission rate should be reflected in a decrease in the ratio of the notification rate in children to that in adults, and serves as a helpful indicator of early case-finding and effective TB infection treatment. However, this will also be influenced by the effectiveness of case-finding activities for children, depending on the trend in the percentage of children missed (i.e. not diagnosed and/or not reported), and may thus not be suited to measure TB programme quality. Increased investment in contact tracing is also supported by the political declaration of the United Nations General Assembly High-level Meeting on TB, held on 26 September 2018, which calls for systematic screening of relevant risk groups for both active and latent TB (20).

To collect and provide the most recent evidence on paediatric MDR-TB relevant for informed decision-making, the WHO Regional Office for Europe has developed this guidance document on MDR-TB in children and adolescents in the Region.

2. Methods, concepts and definitions

This publication was prepared following an extensive, non-systematic, literature search using PubMed and Embase throughout January 2019, using the keywords “tuberculosis (TB)”, “multidrug-resistant tuberculosis (MDR-TB)”, “prevention”, “children” and “adolescents”. Notification rates from countries were retrieved from ECDC/WHO Regional Office for Europe joint reports or routinely reported data. Grey literature and WHO policy documents and guidelines relevant to regional child health and TB were consulted. Additional references were identified by experts in the field. The concepts and definitions used are all retrieved from the WHO’s *Framework towards tuberculosis elimination in low-incidence countries* (16), the *Guidance for national tuberculosis programmes on the management of tuberculosis in children* (21) and the *Definitions and reporting framework for tuberculosis* (22). A first draft was prepared by the Regional Office and a core writing group.

In this publication, “low-incidence countries” are defined as those with a TB notification rate of less than 100 TB cases of all forms per 1 million population per year (23). “Pre-elimination” is defined as less than 10 notified TB cases of all forms per million population per year (24). “Elimination” is defined as less than one notified TB case per million population per year. We follow the *Consensus statement on research definitions for MDR-TB in children* in the terms used for treatment in this publication (25). Terms used for the treatment given to those with TB disease include “curative treatment”, “disease treatment”, “anti-TB treatment” and “TB treatment”. To avoid ambiguity, we suggest using the term “TB treatment”. In the existing literature, there is also inconsistency surrounding the terminology used to describe other forms of chemotherapy. “Pre-exposure prophylaxis” refers to treatment given to a child without known exposure to an infectious TB case. “Post-exposure (including window) prophylaxis” refers to treatment given to a child after documented TB exposure. “Treatment of latent TB infection” refers to drugs given after a positive immunological test result indicating previous or current *M. tuberculosis* infection. “Post-treatment prophylaxis” refers to treatment given to a child after a course of TB treatment. For consistency, we suggest the use of the summative term “TB preventive therapy” or “treatment of infection” to cover all of these circumstances.

Adolescent refers to any person aged 10–19 years (21).

A **child**, unless otherwise specified, refers to the under 15 years age group.

An **infant** is a child aged less than 1 year.

A **close contact** is a person who is not in the household but who shares an enclosed space with the index case for extended daytime periods.

Preventive therapy or “**treatment of infection**” refers to treatment given to prevent disease. A number of at-risk populations are considered for preventive therapy, which includes children and adolescents who are contacts of patients with infectious TB disease but who themselves do not have TB disease.

Latent tuberculosis infection (LTBI) refers to a measurable immune response to TB antigens in whole blood, or a positive skin reaction using the tuberculin skin test (TST) without evidence of active clinical disease. LTBI can be treated by preventive therapy.

Drug susceptibility testing (DST) denotes the *in vitro* testing of clinical *M. tuberculosis* isolates to detect phenotypic (using broth-based methods) or molecular (using line probe, PCR-based, or NGS-based techniques) resistance to an antimicrobial drug.

Polymerase chain reaction (PCR) is a method widely used in the diagnostic laboratory to amplify a specific DNA fragment of interest.

Xpert MTB/RIF is a cartridge-based, almost point-of-care test that provides rapid information on the presence of *M. tuberculosis* and rifampicin resistance using PCR.

Next generation sequencing (NGS), also known as high throughput or massively parallel sequencing, is the process of determining the nucleic acid sequence of the DNA.

Severe disease in children or adolescents is defined by the presence of cavities or bilateral disease on chest radiography or extrapulmonary forms of disease other than lymphadenopathy. In children under 10 years, the occurrence of advanced malnutrition or advanced immunosuppression or positive TB bacteriology may also be considered when determining disease severity.

Immunosuppression refers to a reduction of the efficacy of the immune system through various underlying causes (i.e. immunosuppressive medications, HIV coinfection, malignancies, etc.).

Rifampicin-resistant TB is a disease caused by isolates that are resistant to rifampicin as tested by phenotypic or genotypic DST.

Multidrug-resistant TB (MDR-TB) refers to disease caused by strains that are phenotypically or genotypically resistant to both isoniazid and rifampicin. For some drugs, the relationship between genetic mutations and phenotypic resistance is well understood. The gold standard, however, remains phenotypic drug susceptibility testing.

Extensively drug-resistant TB (XDR-TB) refers to MDR-TB isolates with additional resistance to any of the fluoroquinolones and to at least one of the three injectable second-line drugs (amikacin, capreomycin or kanamycin) (26).

A **source case** is defined as the person who has likely infected the child; an **index case** is referred to as the first case identified by the public health services in the household or the context of an outbreak (27).

In the WHO European Region, **18 high-priority countries** for TB control bear 85% of the TB burden and 99% of the MDR-TB burden: Armenia, Azerbaijan, Belarus, Bulgaria, Estonia, Georgia, Kazakhstan, Kyrgyzstan, Latvia, Lithuania, the Republic of Moldova, Romania, the Russian Federation, Tajikistan, Turkey, Turkmenistan, Ukraine and Uzbekistan.

3. Resources

New practice-based recommendations from a global partnership of researchers, caregivers and advocates of paediatric MDR-TB are providing useful clinical information to manage MDR-/XDR-TB in children and adolescents (28). The field guide by the Sentinel Project on Pediatric Drug-resistant Tuberculosis provides important advice and guidance on managing children and adolescents. This guide has been reviewed by the WHO Global TB Programme for alignment with the updated WHO guidelines. It is clearly indicated where the practical guidance goes beyond what WHO can currently recommend based on the available evidence. This practical guide includes the diagnosis of MDR-TB disease, the construction of MDR-TB regimens, the timing of treatment monitoring, how to deal with adverse events, the management of comorbid conditions such as HIV, how to support treatment adherence, assistance in nutritional monitoring, and the management of MDR-TB child contacts. The WHO Regional Office for Europe encourages the use of this guide for the practical management of MDR-TB in children and adolescents. The Sentinel Project is also happy to offer support and advice via email (tbsentinelproject@gmail.com).

Other sources of expert advice are provided by the paediatric tuberculosis network (ptbnet) and the TB Consilium. TB Consilium is a network with the aim of (i) improving the clinical management of difficult to treat children (e.g. affected by MDR- and XDR-TB), (ii) increasing the probability of favourable outcomes, and (iii) lowering the chances of developing further drug resistance (29). This team links experts with varying backgrounds (e.g. clinical, surgical, public health, microbiology, etc.) and provides rapid clinical advice. Any health-care worker who needs clinical support can ask advice from the Global TB Consilium via email (tbconsilium@gmail.com). Upon completing anonymized patient forms the physician will receive rapid clinical advice within 48 hours from two selected global TB experts and consolidated by a clinical coordinator.

Ptbnet is a network of European paediatric TB experts and provides advice on difficult to treat paediatric MDR-TB cases. The members of the network can be contacted via email (ptbnet@googlegroups.com).

4. Specific aspects of MDR-TB in children and adolescents in the WHO European Region

Since 2008, activities related to TB prevention, care and surveillance in the European Region have been coordinated jointly by the ECDC and the WHO Regional Office for Europe, and cover the 53 countries of the Region. The Region carries about 3% of the global TB burden (1), which is distributed unevenly across the Member States. The majority of this burden (about 85%) originates from 18 high-priority countries: Armenia, Azerbaijan, Belarus, Bulgaria, Estonia, Georgia, Kazakhstan, Kyrgyzstan, Latvia, Lithuania, the Republic of Moldova, Romania, the Russian Federation, Tajikistan, Turkey, Turkmenistan, Ukraine and Uzbekistan.

In recent years, the incidence has fallen at a rate of 4.4% per year. There were 410 000 cases in the Region in 2007 compared to 290 000 in 2016. Despite seeing the most rapid decline in any WHO region worldwide, incident TB cases need to be further reduced in the Region to meet the targets set out in the Roadmap to Implement the Tuberculosis Action Plan for the WHO European Region 2016–2020 (10). It is estimated that 1 in 5 cases of MDR-TB globally occurs in the Region, which illustrates the high burden of drug resistance faced by Member States, of which 9 are grouped in the 30 countries with the highest MDR-TB rates globally.

WHO estimates that in 2016, 19% of newly diagnosed cases, as well as 55% of relapse or previously treated cases of TB in the Region were MDR-TB (1). Three broad groups can hence be defined in the Region: (i) low-incidence countries with cases among the most vulnerable groups, (i.e. young children, individuals living with HIV or other immunocompromising conditions, or people migrating from high-incidence countries); (ii) countries with moderate incidence and low rates of MDR-TB; and (iii) countries with high incidences of drug-susceptible TB and MDR-TB but with declining TB rates in general (19).

All global goals and targets in the Millennium and later Sustainable Development Goals relevant to TB prevention and care have been endorsed by the countries of the European Region. Yet, even with all these commitments, it has become clear that the Region will not be able to eliminate the disease by 2050, as is laid out in these targets. Calculation of the average annual rates of change for TB incidence to meet the grand convergence targets set out by the independent Lancet Commission “Global Health 2035: a world converging within a generation” illustrates that the current average annual rate of decline is 4.6 per 100 000 population, below the required rate in Eurasia and the Mediterranean (30). In recognition of this, the Berlin Declaration was drafted during a Ministerial Forum organized by the WHO Regional Office for Europe in 2007, to undertake actions that strengthen public health systems and TB relevant services. The ECDC then developed a framework for action to combat TB as five of the high-priority countries are members of the European Union.

The eight strategic areas of the Framework Action Plan to Fight Tuberculosis in the European Union (31) were (i) TB prevention and care commitment, TB awareness, and capacity of health systems; (ii) surveillance; (iii) laboratory services; (iv) prompt and quality TB care for all; (v) MDR- and XDR-TB; (vi) TB/HIV coinfection; (vii) new tools for TB prevention and care; and (viii) building partnership and collaboration with countries (19,31).

Recent surveys have investigated the preparedness of European countries based on these eight strategic areas (7,32,33). One survey of national TB programmes found that only half (55%) of European Union/European Economic Area countries reported having a national TB strategy (33). With regards to child and adolescent TB, only 25% of the WHO European Region Member States had dedicated guidelines in place (7). This illustrates the continued need to provide guidance and support to Members States in designing, implementing and evaluating national TB guidance documents, notably for child and adolescent TB.

In the European Region, children with TB or at risk of TB do not routinely enter the health systems through classical TB programmes, owing to the low incidence of TB in most countries in the Region and the challenging diagnosis of TB. Given the broad clinical presentation of different forms of childhood TB, children usually present to family doctors, emergency departments or general paediatricians, where TB is among the differentials. When children are contacts of a TB source case, families are contacted by public health services and invited to attend health centres for evaluation of TB disease and infection. The vertical health systems structure in many Member States with highly specialized health services may lead to misdiagnosis and mismanagement of MDR-TB patients. Therefore, a horizontal approach ultimately featuring universal health coverage as well as intersectoral collaboration has been advocated for (34,35).

In summary, there is still a need to develop national TB guidance documents in some countries of the European Region, in particular those dedicated to child and adolescent TB, to achieve the goals set out in recent political commitments towards health.

5. Epidemiology of child and adolescent MDR-TB

WHO has been collecting data on isoniazid and rifampicin resistance, stratified by age group, since 1994 (36). In the years 1994–1999, no cases of MDR-TB in children and adolescents were reported. In 2000–2011, 35 countries reported at least one case of MDR-TB among children under 15 years of age. Estimating the burden of MDR-TB among children and adolescents is essential to identify existing knowledge and treatment gaps (37).

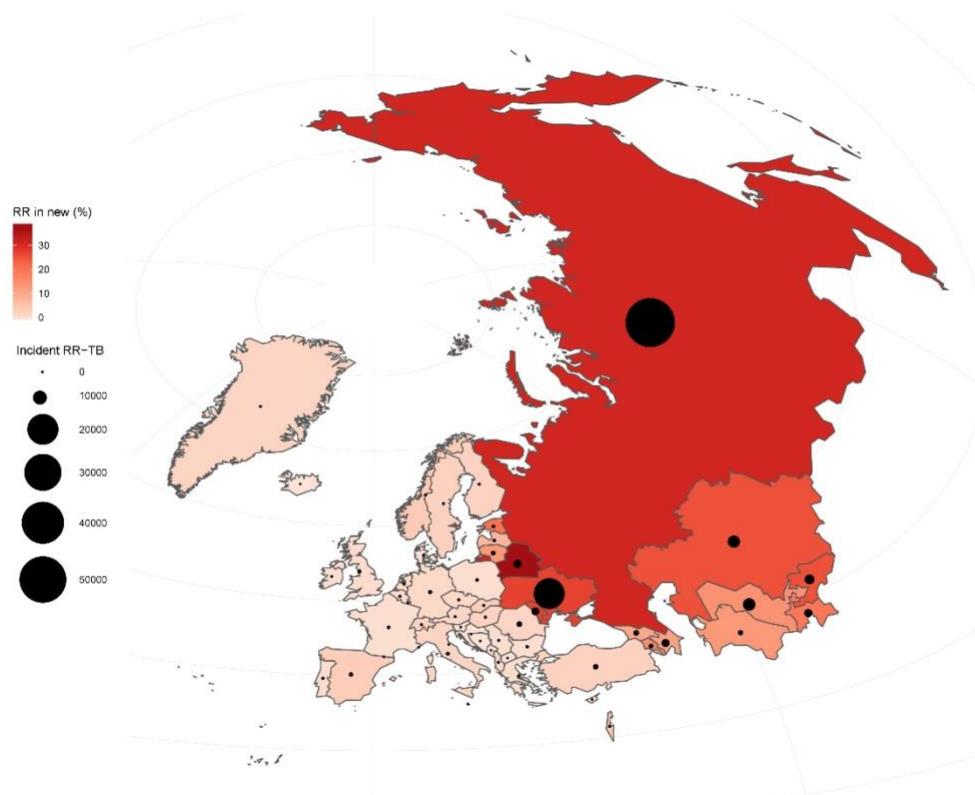
Confirming the diagnosis of MDR-TB in young children is difficult and estimates of the prevalence of MDR-TB among young children rely on modelling studies. However, it is well recognized that young child contacts are at high risk of disease following infection, irrespective of whether they are infected with *M. tuberculosis* that is drug-resistant or drug-susceptible. A study from South Africa evaluated the prevalence of TB infection and disease in 125 children with MDR-TB household contacts, who were followed for 30 months, and found that 78% of children were either infected or developed disease (38). However, not all children with MDR-TB will have an identifiable contact with MDR-TB, which adds to the challenges of detection and treatment. The likelihood of being able to identify the source case will rely on a number of factors, and will vary between low endemic settings and high endemic settings where transmission outside the household or family environment will be relatively more common.

In 2010, approximately 15% (5000) of the overall MDR-TB burden the WHO European Region was in children, according to estimates published in the Lancet; while the largest regional childhood MDR-TB incidence was found in the WHO South-East Asia Region, with about 10 000 children (see Fig. 1) (3). Looking specifically at isoniazid resistance among children through a systematic literature search, an estimated 12.1% of children with TB were infected with an isoniazid-resistant strain in 2010 (39). The European Region was found to have a rate of isoniazid-resistance of 26.1%. By combining mathematical modelling with available drug resistance patterns, another team calculated the proportions of MDR-TB for each country and WHO region (40). In 2014, a total of 6.9% of incident TB cases were isoniazid-monoresistant, and 2.9% were multidrug resistant, with pronounced variation among the WHO regions. The estimated number of children with MDR-TB in the European Region was 2120 (16% of the total of 13 500 incident cases) in that year (40). A more recent modelling study suggests that 14.1% of latent TB infection in children younger than 14 years is multidrug resistant, a much higher proportion than in adults (2.8%) (41).

5.1 Reported incidence of TB and MDR-TB among children

The most recent reported numbers from the ECDC and the WHO Regional Office for Europe are based on 2017 data. Among the TB cases and relapses, there were 3421 children under the age of

Fig. 1. Estimated burden of rifampicin-resistant tuberculosis in children in 2017



RR = rifampicin resistant.

Note: The figure illustrates both the total number of incident rifampicin-resistant TB cases (size of the black circles per country), and the percentage of all new reported TB cases that are rifampicin-resistant (colour coded per country) in the WHO European Region. Data taken from the Global Tuberculosis Report 2018 (1).

Source: Peter Dodd, University of Sheffield, personal communication, 2019.

5 years, and 6269 aged 5–14 years, making a total of 9690 childhood TB cases reported in year 2017 in the European region, comprising the 53 countries of the WHO European Region and Liechtenstein (18). This represents about 4% of total notified TB cases across all ages in the Region. The 18 high-priority countries accounted for 82% of notified paediatric TB cases. In these countries the rate of TB in children under 5 years was lower than the notification rate among children aged 5–14 years, which suggests under-detection and diagnosis of children under 5 years with TB disease (18). The case-notification rate of new cases and relapses in children under 5 in the WHO European Region was 6.0 per 100 000 population, and 5.7 per 100 000 for children aged 5–14 years in 2017. The 2018 WHO *Global Tuberculosis Report*, based on 2017 data, documented 21 000 cases worldwide of TB in children under 15 years (1).

The case detection rate provides a useful estimate of treatment coverage. The total estimated burden in children in the WHO European Region of 21 376 (10 646 aged 0–4 and 10 730 aged 5–14 years) yields a case detection rate of 32.1% for children aged 0–4 years, 58.4% for children and young adolescents aged 5–14 years, and a total (0–14 years) of 45.4%, in line with the global average (1).

5.2 Treatment outcome

In 2015, 5167 (93.5%) of the 7215 notified childhood TB cases in the European Region were successfully treated (18). There were 71 deaths (1% of all cases) reported, 56 (0.8%) who failed treatment and 103 children (1.4%) lost to follow-up. The remaining 317 cases (4.4%) were reported as not evaluated. An international collaborative group performed individual patient data meta-analysis to elucidate treatment outcomes in children with MDR-TB (13). Data from 18 countries were analysed that included 975 children with MDR-TB (75% bacteriologically confirmed and 25% clinically diagnosed). Among this cohort, the median age was 7.1 years. HIV coinfection was present in 39% of children. Overall, 764 of 975 (78%) cases were reported to have a successful treatment outcome at the conclusion of therapy. Treatment success was only 56% in HIV-positive children with MDR-TB who were not treated with antiretroviral therapy (ART) compared to 82% in HIV-positive children who received ART. In general, this study provides robust evidence that children with MDR-TB generally respond well to therapy, and underlines the importance of ART for HIV-positive children with TB (13). An earlier systematic review of eight studies, covering 315 children with MDR-TB, reported treatment success in 82% of cases, with 5.6% deaths and 6.2% defaults (12). These studies provide evidence that MDR-TB can be successfully treated in the majority of children.

In order to further ensure treatment success for children and adolescents with MDR-TB, efforts should be made to implement individual electronic reporting throughout the WHO European Region to provide more reliable reporting of cases (Box 1). This would allow accurate and timely notification of DR-TB cases in children and adolescents. Subsequently, treatment outcomes of DR-TB in this particular group should also be reported.

Box 1. Key elements for consideration to improve childhood MDR-TB reporting

- Strive for accurate and timely notification of DR-TB in children and adolescents.
- Report MDR-TB cases in children and adolescents more reliably.
- Report treatment outcomes of DR-TB in children and adolescents.
- Ideally, reporting should be done through individual electronic reporting throughout the entire WHO European Region.

6. Key guideline documents for the regional response to child and adolescent MDR-TB

The global and regional TB and child health community has increasingly recognized child and adolescent TB as an important health threat. The first international meeting on child and adolescent TB was jointly organized by the ECDC and the Stop TB Partnership and held in Stockholm in 2011. World TB Day was dedicated to children for the first time in 2012 (7,42). To identify challenges and key priorities in the global response to child and adolescent TB, two dedicated roadmaps have been developed. The first, entitled *Roadmap for Childhood Tuberculosis: Towards Zero Deaths*, was published in 2013, and declared the goal of a world without TB deaths among children (43). It outlined 10 key actions to be taken both at global and national levels to mitigate the burden of child and adolescent TB, including the specific needs in research, policy development and clinical practice.

While significant progress has been made since the first roadmap, key challenges and missed opportunities are discussed in the 2018 follow-up, the *Roadmap Towards Ending TB in Children and Adolescents* (44). It points to insufficient advocacy, political leadership and stakeholder engagement in the response to child and adolescent TB, evidenced by the many TB programmes of high-burden countries being dependent on external funding. It also identifies policy-practice gaps in scaling up preventive measures such as contact tracing of affected children and adolescents (44). The 2018 roadmap finally calls for a family- and community-centred strategy to better integrate child and adolescent care. It pinpoints several bottlenecks along the child's pathway from first TB exposure to development of TB disease where improved service delivery can yield better detection and help achieve improved cure rates. This roadmap also emphasizes the importance of multisectoral accountability in line with the recently drafted TB multisectoral accountability framework (45). The roadmap equally notes a lack of joint accountability and resulting verticalization of the TB response as major missed opportunities in the past and proposes the fostering of national leadership and accountability as key actions in the future. In 2018, another technical document entitled *Guiding principles to reduce tuberculosis transmission in the WHO European Region* was published, which specifically addresses children in recommendations and policy options to reduce TB transmission (46).

The region-specific activities and priorities of the WHO Regional Office for Europe are informed by the Consolidated Action Plan to Prevent and Combat Multidrug- and Extensively Drug-resistant Tuberculosis in the WHO European Region 2011–2015 and the follow-up Tuberculosis Action Plan for the WHO European Region 2016–2020, as decided by the WHO Regional Committee for Europe (14,15). The Consolidated Action Plan asks Member States to “develop a special response for TB prevention and control in children” (14). It further requires its members to incorporate updated child and adolescent TB guidelines by mid-2012. The Tuberculosis Action Plan, building on the

Consolidated Action Plan, emphasizes that Member States should regularly update “childhood tuberculosis guidelines ... according to the latest available evidence and WHO recommendations” (15).

Beyond the regional actions plans, general WHO recommendations are summarized in the *Guidance for national tuberculosis programmes on the management of tuberculosis in children*, with the first edition published in 2006 and a second edition in 2014, with a greater focus on MDR-TB than the first edition (21). This provides all Member States with comprehensive information on diagnosis, treatment and prevention of child and adolescent TB, including chapters devoted to managing TB/HIV coinfection as well as drug-resistant forms of TB in children and adolescents. This is of particular relevance to the WHO European Region as it includes those Member States affected most by DR-TB, as well as rising incidences of coinfection with HIV. The recently updated WHO guidelines on LTBI management (2018) include guidance on the management of contacts of MDR-TB cases, which includes the consideration of providing preventive therapy (or treatment of infection) for “high-risk” household contacts of patients with MDR-TB (47). Currently, the WHO Regional Office for Europe is in the process of finalizing a European guidance document on LTBI and TB elimination, adapted to the context of the European Region.

Finally, the resolution adopted by the United Nations General Assembly High-level Meeting on TB contained a strong political declaration to end TB and dedicated several sections to children and adolescents (20). In addition to recognizing the importance of addressing childhood illness and death, as well as HIV coinfection, it also highlighted the significance of providing support to caregivers and the availability of child-friendly drug formulations.

In summary, the many available guidance documents published in the recent past testify that child and adolescent TB now receives substantially more attention than before in the European Region and elsewhere. In the European Region in particular, a continued effort should be made to ensure that Member States regularly update their childhood TB guidelines according to the latest available evidence and WHO recommendations. Efforts should also be made to ensure that these guidelines, once developed are implemented effectively.

7. Particularities of diagnosing and treating MDR-TB in children and adolescents

Despite children and adolescents accounting for 26% of the global population, and 42% of the population in low-income countries, research and development into child and adolescent TB has been neglected (6,48). This is chiefly due to greater challenges in diagnosis and the lower priority traditionally given to this group by TB prevention and care programmes.

The disease presentation in children and adolescents can mimic several common diseases, hence TB is often not considered in the differential diagnosis, especially in low-burden settings or in young children. Following infection, young children and adolescents are at high risk of progression to TB disease, and there are particularities distinct to paediatric patients. Bacteriological confirmation of TB disease in children is challenging, with a lower diagnostic yield from microscopy, culture and molecular tests than in adults due to the paucibacillary nature of the pathology, particularly in young children (49,50). It is also challenging to obtain biological specimens in children, especially in younger children who are unable to spontaneously expectorate and who have paucibacillary disease. Promising research is emerging to diagnose TB in stool samples, with high concordance between Xpert MTB/RIF from sputum and stool specimens (51,52). Despite these recognized challenges, WHO recommends “bacteriological confirmation whenever possible” and this is particularly relevant for the assessment of a child with possible or presumptive MDR-TB.

Nonetheless, bacteriological confirmation may not be possible or may be delayed, so most children will require a decision to treat for TB to be made on the basis of a clinical diagnosis, based on careful history taking (including all contacts with a TB case), a thorough examination and nutritional assessment, and further investigations depending on the site of presentation, such as chest X-ray or lymph node aspiration, and HIV testing (21). Although this is still common practice, a trial TB treatment should not be used to make a diagnosis (53).

All children diagnosed with TB should be registered with the national TB programme. Further, the detection of TB in a child should lead to investigation of a possible source case (if not yet identified) as this can result in detection of an infectious case in the community requiring treatment.

Young children typically progress rapidly from infection to disease, while adolescents are more likely to develop an adult-type TB. Active surveillance data from the pre-chemotherapy era suggest that most children developed radiological abnormalities following infection, including 60–80% of children under 2 years of age (54). On the other hand, pre-adolescent children older than 4 years of age have lower rates of progression to TB disease following infection than adolescents or adults (6,54,55). Due to the immaturity of the immune response, young children are more prone to developing

extrapulmonary TB than adults, although pulmonary TB is still the commonest form. Young children with pulmonary TB are also much less likely to be infectious than adolescents or adults with this form of the disease due to a lower bacillary load and less cough force (56,57).

Approximately 20–30% of TB cases in children have extrapulmonary manifestations (58). Miliary TB is one of the most serious forms, resulting from the haematogenous dissemination of *M. tuberculosis*, increasing the risk of TB meningitis, which occurs in 20–30% of cases of miliary TB (55,59). A major benefit of Bacillus Calmette–Guérin (BCG) immunization is that it significantly reduces the risk of severe, disseminated forms of TB in infants and young children (60,61).

Although young children with TB are not a group responsible for most of the ongoing transmission in the community, older children and adolescents who have adult types of TB disease, are more likely to transmit it. This is important to consider as the lower public health priority given to childhood TB is in part due to the assumption that children and adolescents play a minor role in transmission. Children do develop and can transmit MDR- and XDR-TB (62). MDR-TB in children, especially in those less than 5 years of age, is usually a primary disease following recent infection. Therefore, surveillance of drug resistance in children can provide an indicator of transmitted *M. tuberculosis* strains that are currently circulating in a community (63). Studies have shown that DR-TB trends in adult populations are soon followed by the same trends in children and adolescents (64,65).

Nevertheless, improving treatment for MDR-TB in children and adolescents remains challenging. Clinical trials are usually done in adults with microbiologically proven pulmonary TB, allowing objective microbiological case definitions and treatment outcomes. Since such case definitions and treatment endpoints are often impractical in children and adolescents, few clinical trials have been conducted in children to establish optimum anti-TB treatment regimens (6,66). While data on pharmacokinetics is available for delamanid in children of all ages and bedaquiline for children as young as 6 years, current treatment guidelines for children with MDR-TB are largely inferred from adult data. Until recently, there were few second-line drugs for MDR-TB available in formulations suitable for children, such as dissolvable tablets with a pleasant taste, or tablets formulated as fixed-dose combinations. Although, these formulations increasingly exist, they are often sold at very high prices and are not available at the sites that they are needed.

Aside from children, consideration should also be given to pregnant women and newborns. Pregnancy is associated with an increased risk of progression from TB infection to disease, notably in the last trimester and the early postnatal period (21). Pregnancy-related TB is associated with risks to the fetus and newborn, as well as to the mother, and there is the additional risk of toxicity associated with the use of drugs to treat MDR- or XDR-TB. Disseminated TB occurs in 5–10% of pregnant women suffering from TB, and this presents a particular risk for congenital TB (67). Likewise, newborns can

also acquire TB after birth through exposure to a contagious mother or another close contact, which is termed “neonatal TB”. Knowledge about the safety of MDR-TB drugs, including new drugs such as bedaquiline and delamanid, in pregnancy and while breastfeeding is still sparse (26).

In summary, there are particularities distinct to paediatric patients which need to be considered in the diagnosis and treatment of MDR-TB in children and adolescents. More public health priority should be given to childhood TB considering the current knowledge of children’s contribution to transmission. In addition, an increased awareness should also be given to pregnancy-related TB, taking into account its associated risks to the fetus and newborn.

8. Diagnosis and treatment of MDR-TB infection in children and adolescents

The following sections heavily draw on previous work by the Sentinel Project on Pediatric Drug-resistant Tuberculosis (68,69), the WHO *Guidance for national tuberculosis programmes on the management of tuberculosis in children* (21), and the most recent WHO guidelines on managing MDR-TB (26) and on the management of LTBI (47).

8.1 Assessment of children and adolescents exposed to MDR-TB

The initial assessment of a child or adolescent that has been exposed to a source case with any form of DR-TB consists of careful history taking, a thorough physical examination and chest radiography. This assessment is described in more detail in Section 9 on diagnosis and management of MDR-TB disease. Once TB disease has been ruled out, a decision should be made regarding whether the child or adolescent should receive TB infection treatment. The final decision belongs to the clinician, in partnership with the patient and/or caregiver, who also needs to decide which drugs should be given for this treatment, as specified further below. This decision to treat for infection will include consideration of the risk of the child or adolescent developing disease following exposure. If available, a test should be performed to evaluate for infection.

Tests for infection include TST and the interferon- γ release assay (IGRA). For the TST, purified protein derivative (PPD) is injected intradermally into the forearm and the skin reaction is read after 48–72 hours. The reaction is measured laterally (i.e. perpendicular to the long axis of the forearm) in millimetres and should assess only the induration and not the redness (erythema). The test result helps the caregiver to evaluate the risk of infection, in conjunction with a clinical assessment of the probability that the child or adolescent has been infected with *M. tuberculosis*. The IGRA has advantages in specificity over the TST, as it is able to differentiate between exposure to *M. tuberculosis* complex members and previous BCG vaccination. This is facilitated through the use of stimulating antigens in the assay that are deleted in the BCG vaccine strains (70). IGRA is also able to distinguish between infection with *M. tuberculosis* and non-tuberculous mycobacteria. In addition, IGRA only requires one clinical visit, as opposed to the two required for TST (placing the PPD and then reading it).

A systematic review of 17 published reports, of which 5 were in children and adolescents, identified studies with contradictory results between IGRA and TST in identifying TB infection, with poor performance of these tests among the youngest children, and those with HIV coinfection, and malnutrition (71). However, the true clinical value of IGRA lies in its prognostic value for future TB disease, although it should be emphasized that neither of these tests are validated for this use.

Commercial IGRAs have a higher positive predictive value (PPV) for progression of TB infection to TB disease when compared to TST, although it should be noted that only a little evidence exists for children in this regard (72). Notably, in low-incidence settings, like most Member States of the WHO European Region, the PPV of IGRA in contacts recently exposed to TB index cases was superior to that of TST, although data is still lacking in children younger than 2 years (73). Given the limited data on the sensitivity and specificity of IGRA for young children, we conclude that IGRA can be used over TST in children 5 years or older who are immunocompetent and have a history of BCG vaccination. It may be considered in those above 2 years of age (74–77).

8.2 Contact tracing or post-exposure management

Once a source case has been identified, investigation of contacts should be a priority for national TB programmes. Household contacts are a high-risk group for developing TB, notably within the first year, and screening first in this setting is likely the most efficient approach (78). Contact investigation comprises a systematic screen among all contacts of the source case, a known TB patient, to identify cases of TB disease or those with TB infection. It involves clinical investigation as well as testing for TB infection and, where possible and indicated, chest radiography and microbiology. Usually, close contacts are screened first (i.e. household members) and subsequently less frequent contacts.

8.3 Managing children and adolescents exposed to MDR-TB – treatment for infection

It is recommended that the decision to treat for infection be based on an individualized risk assessment. As infants and young children (under 5 years) are at high risk of progression from infection to disease, and as TST and IGRA are less reliable in these younger children, significant recent exposure alone, such as close contact in the household or nursery, may be sufficient in this age group for a decision to be made to commence TB infection treatment, although this is not recommended by current WHO guidelines (47). When disease develops, rapid progression and late onset of treatment result the highest mortality rates, and the safety of drugs used for treatment of infection is well established. A test for infection should always be done, if available, but a negative result following recent exposure may not rule out infection.

For young children with low risk from exposure (for example brief contact outside the household or nursery setting) and for children older than 5 years, the decision to treat for TB infection should be based on a positive TST or IGRA, if available, following exclusion of TB disease (47). If unavailable, and exposure has been significant, health-care workers may still decide to provide infection treatment, based on individualized risk assessment.

The following treatment recommendations are based on expert opinion and do not necessarily reflect WHO recommended treatment guidelines (47). Treating TB infection that is presumed to be caused by multidrug-resistant organisms is challenging as limited evidence is available. Although there is some logic for the use of high-dosage isoniazid in cases where the isoniazid resistance has been caused by an *inhA* promoter region mutation, there are limited data to support this. Some preliminary data from Peru, albeit with small numbers of young children included, suggests that isoniazid may have a place in MDR-TB infection treatment (79). However, a growing body of observational data suggests that second-line drugs should be used to treat MDR-TB infection, with a recent systematic review and meta-analysis demonstrating a large risk reduction with the use of these drugs (80). Three large clinical trials are currently in advanced planning or underway, using either levofloxacin or delamanid, daily for six months, in the intervention arm. If a clinician decides to treat MDR-TB infection in a child or adolescent, they should use either a later generation fluoroquinolone (i.e. levofloxacin or moxifloxacin, unless the source case is known to be resistant) alone or in combination with another drug to which the strain from the source case is susceptible. Given the limited safety data on the use of fluoroquinolones in children, caution is advised when using these agents in this population, with periodic monitoring for adverse effects (81–83). Optimal treatment duration is unclear, but 6 months of daily therapy is commonly used. Whether or not the exposed child or adolescent is treated for MDR-TB infection, they should be closely followed up for two years to diagnose the development of disease early (47).

9. Diagnosis and management of MDR-TB disease in children and adolescents

9.1 Making a diagnosis of MDR-TB disease

MDR-TB in children and adolescents can either be bacteriologically confirmed or clinically diagnosed (Box 2). A confirmed diagnosis is based on a combination of features consistent with TB disease (including symptoms, signs and radiology) and a sample taken from the child that demonstrates the presence of *M. tuberculosis* (genotypic or phenotypic) that is resistant to both isoniazid and rifampicin (detected either phenotypically or genotypically).

Children can be clinically diagnosed with MDR-TB if they have a combination of features consistent with TB disease (including symptoms, signs and radiology) and:

- have been in close contact with a source case who has MDR-TB – probable MDR-TB disease; or
- have been in close contact with a source case who has TB disease and risk factors for drug resistance (failed therapy, retreatment, died) – possible MDR-TB disease; or
- have failed a first-line TB regimen in which there was good adherence – possible MDR-TB disease.

Given that the majority of TB disease in children is not confirmed, most children treated for MDR-TB will need to be clinically diagnosed.

Symptoms, signs and radiology for MDR-TB disease in children and adolescents are identical to those of drug-susceptible TB. Pulmonary disease in older children and adolescents is more likely to be adult-type TB with typical symptoms of chronic cough with sputum expectoration, weight loss and fever. Symptoms of pulmonary disease in younger children are frequently less specific, and although also including weight loss, cough and fever, may also include more acute symptoms, wheezing, non-specific lethargy and ill health. Chest radiographs in younger children most commonly reveal intrathoracic lymphadenopathy but can also show non-specific parenchymal changes. As children become older, they more commonly develop radiological signs in keeping with adult-type disease, including pleural effusions, cavities and breakdown.

Extrapulmonary disease also needs to be considered and TB can occur in almost any body site. Miliary TB and TB meningitis are more common in younger children, as compared to older children and adolescents. TB meningitis can present with a chronic prodrome of weight loss, lethargy and fever, but often with an acute presentation of reduced level of consciousness, meningitis signs or seizures. Cervical lymphadenopathy is also more common in younger children, as compared to older

children and adolescents. Where resources allow, ultrasonography, magnetic resonance scanning and computerized tomography scanning are increasingly being used to help with the diagnosis of TB disease in children.

9.2 Sample collection

Clinicians should make every effort to confirm the diagnosis of MDR-TB in children and adolescents, and at least two (but the more the better) clinical samples should be collected. Once samples are obtained, and if the children or adolescents fulfil the criteria for possible or probable MDR-TB, then treatment should be initiated at that point, while waiting for microbiological results. If the sample is tested using recommended molecular tests (Xpert MTB/RIF), then waiting time should not be longer than one day. Children from the age of 5 or so are often able to expectorate sputum and for children and adolescents above this age, suspected of having pulmonary TB, at least two expectorated samples should be collected. However, even in older children and adolescents, using hypertonic saline to induce cough has been associated with increased chance of microbiological confirmation. Younger children suspected of having pulmonary TB require respiratory samples to be collected using gastric or nasopharyngeal aspiration or induced sputum sampling. Children and adolescents suspected of having extra-pulmonary TB, should have alternative samples taken, dependent on site of disease (cerebrospinal fluid, lymph node aspiration biopsy, tissue biopsy etc.). In all children and adolescents, full infection control precautions need to be taken when obtaining clinical samples.

Using stool for Xpert MTB/RIF testing could provide an equally reliable and easier method to obtain bacteriological diagnosis of TB in children, although it is not currently recommended by WHO. Importantly, a negative stool test should never rule out disease. Clinical test performance among 166 pulmonary TB and asymptomatic TB child household contacts was promising in a recent study where 95% (22 out of 23) of stool samples yielded positive results for culture-positive cases (51). Using a simplified two-step processing method on stool samples, another study equally achieved high concordance between Xpert MTB/RIF results on stool and respiratory samples (52).

Samples collected should be processed in the laboratory using liquid culture and molecular tests. Culture remains the “gold standard” and has higher yields than novel molecular tests. However, molecular tests can provide results within hours rather than weeks and should therefore be performed in all paediatric samples for initial diagnosis. All tests should be done in laboratories participating in quality control schemes. A negative bacteriological result, however, does not exclude the diagnosis of either extra-pulmonary or pulmonary MDR-TB in children. If there is strong clinical suspicion based on the history, symptoms, radiology, and resistance profile of the strain from the identified source case, then the child should be treated for MDR-TB.

9.3 The role of molecular tests for diagnosis of drug-resistance

Molecular tests aim to identify genetic mutations that reliably predict resistance and can be used to initiate targeted treatment without the long waiting times required for mycobacterial growth in culture (84). These WHO-recommended tests have considerable advantages for the scale-up of programmatic management and the surveillance of MDR-TB (85). Line probe assays were the first molecular tests widely implemented in the diagnosis of TB and MDR-TB (86,87). The GenoType MTBDR*plus* enables rapid resistance prediction by interrogating the *rpoB* gene conferring resistance to rifampicin, as well as the *katG* gene and the promoter region of *inhA*, responsible for isoniazid resistance (88). Another WHO-recommended line probe assay widely used is the GenoType MTBDR*sl*, which targets genes responsible for resistance to second-line drugs.

A systematic review and meta-analysis evaluated the diagnostic accuracy of these tests and found very high pooled sensitivities and specificities for rifampicin, and variable performance for isoniazid (89). Numerous studies have looked at the diagnostic accuracy of these line probe assays for specific drugs. High sensitivities and specificities were observed to detect resistance to fluoroquinolones (90,91), an overall 81% sensitivity and 100% specificity to genotypically diagnose MDR-TB, and 50% sensitivity and 97.6% specificity to diagnose XDR-TB (92). The Xpert MTB/RIF, a semi-automated real-time PCR-based “close-to-point-of-care” test is able to diagnose TB and rifampicin resistance within two hours from sputum samples. Xpert MTB/RIF is able to accurately detect TB and rifampicin resistance with 100% sensitivity and 98.3% specificity compared to culture in low-incidence settings (93). A systematic review specifically looking at the performance of GeneXpert in diagnosing pulmonary TB in children found pooled sensitivity of 62% and a specificity of 98%, compared to culture, where the Xpert MTB/RIF’s sensitivity was 36–44% higher than sputum microscopy (94).

Xpert MTB/RIF was widely rolled out upon WHO endorsement and its success led to the development of the next-generation Xpert MTB/RIF Ultra assay. This amplifies additional molecular targets, provides increased sensitivity on a smaller number of bacilli and returns results in less turnaround time. Head-to-head comparison of the diagnostic accuracy of Xpert MTB/RIF Ultra and classical Xpert MTB/RIF showed that Xpert MTB/RIF Ultra yields higher sensitivities in low-incidence settings, such as the WHO European Region, and for people living with HIV as well as TB meningitis (95). This is yet to be verified in children in high incidence settings. One particular challenge of the new Xpert MTB/RIF Ultra is the interpretation of a “trace” result. It should be noted that a trace result, in a child investigated for TB symptoms, or an abnormal chest X-ray, is unlikely to be a false positive. Given the implications of re-testing and delaying a diagnosis, it is suggested that this be considered positive, unless there is good reason to suspect otherwise.

The Framework of Indicators and Targets for Laboratory Strengthening under the End TB Strategy presumes that in 2020, Xpert MTB/RIF will be the initial diagnostic test for all people living with HIV and clinical signs of TB, all children with signs of TB, all patients at risk of MDR-TB, and 80% of previously untreated HIV-negative adults with symptoms of TB, as well as all new TB cases as a drug-susceptibility test (96). WHO, in the latest *Guidance for national tuberculosis programmes on the management of tuberculosis in children*, puts forward recommendations regarding the clinical use of Xpert MTB/RIF (21). In summary, Xpert MTB/RIF provides advantages over smear microscopy and, given the rapid turnaround time, can also provide results much earlier than culture, especially in many situations where culture is not available. Xpert MTB/RIF has been found to be less sensitive than culture in studies done to date in children, and therefore if culture is available, it is advisable to split samples and test with both Xpert and culture.

9.4 The role of DNA sequencing for child and adolescent MDR-TB

The increasing use of molecular tools to diagnose MDR-TB and characterize the resistance profile of the infecting organism enables more targeted and individualized treatment regimens (97). The advent of next generation sequencing (NGS) to obtain the whole genome sequence of the infecting strain in a timely and cost-effective manner has allowed us to increase our knowledge of mutations associated with resistance (85). Whole genome sequencing (WGS) allows characterization of all known genes conferring resistance, and the absence of resistance-associated genes in turn is a reliable biomarker for drug susceptibility (98–100). A recent analysis of genotype-phenotype correlations of more than 10 000 mycobacterial genomes has shown that WGS can reliably predict susceptibility to first-line drugs (101). As a consequence, the United Kingdom was the first country of the WHO European Region to roll out routine WGS of TB for diagnosis and resistance prediction (102). Pioneering population-based use of this new technology will help to establish solid resistance mutation catalogues linked to phenotypic resistance and treatment outcomes. WHO and FIND have developed a guidance document on the use of NGS in the diagnosis and resistance prediction of resistance-conferring mutations (103). The NGS approach prevails over other diagnostic and resistance-testing technologies by providing rapid and detailed sequence information for the whole genome. This approach can also be used for targeted sequencing of selected genes that are known to be involved in resistance, or to detect the presence of both susceptible and resistant bacterial strains in one patient (i.e. hetero resistance). At present, uptake and integration of NGS in routine diagnosis is still limited by the need for sophisticated bioinformatic analyses.

One of the hurdles in the use of this technology is that direct sequencing from patient sputum specimens remains challenging (104). However, reports are accumulating that document ways of overcoming these challenges. By using targeted DNA enrichment, antibiotic susceptibility profiles were obtained within five days of sample receipt, compared to 29 days by liquid and 36 days by solid

culture (105). Another report corroborates that rapid molecular resistance prediction is possible through NGS application (106). By analysing 328 culture-positive TB isolates, WGS allowed generation of DST results within 72 hours of sample receipt compared to 28 days with liquid culture. Although this technique needs further refining and simplification, the potential of NGS in child and adolescent TB diagnostics and resistance prediction is promising.

Box 2. Key elements for consideration regarding diagnosis and treatment of TB infection and disease

These suggestions and other recommendations throughout the document need to be regularly updated as new evidence emerges.

TB infection diagnosis

- Conduct contact investigation.
- Use interferon-gamma release assays or TST, where available, in line with recent WHO recommendations.
- Treat with WHO-recommended regimens.
- Create a register to monitor individuals treated for DR-TB.

Management of TB infection

- Rule out TB disease.
- Treat TB infection.
- Ensure monitoring and evaluation: TB infection registers, description of the TB infection cascade including treatment completion rates.

TB disease diagnosis

- Sensitize child and family physicians to be more aware of TB in children and adolescents.
- Make all efforts to confirm TB bacteriologically (gastric or nasopharyngeal aspirate, bronchoscopy, materials for extrapulmonary lesions, direct smear, culture, DST, Xpert).
- Perform radiology (chest X-ray) where available.
- If all efforts have been made and the diagnosis is not confirmed, the child should be treated based on clinical and/or radiological findings and the DST pattern of the source case.

TB disease treatment

- Adopt updated guidelines and recommended regimens and doses (noting recent changes).
- Employ child-friendly and child-specific formulations whenever possible (ideally dispersible).

9.5 Treatment of MDR-TB disease

The recommended regimens to treat MDR-TB in children have undergone some fundamental changes within the last five years (Box 3). When designing a regimen for the treatment of MDR-TB in children or adolescents, decisions should be guided by DST on the isolate from the child/adolescent, or, if clinically diagnosed, by the pattern of resistance from the source case (57). The treatment history of both the child and the source case should be incorporated to evaluate the effectiveness of drugs when DST is unavailable or unreliable. If certain resistances are known to be prevalent locally this

should also be considered in treatment regimen design. In 2019, WHO re-ordered the available anti-TB drugs (Table 1) and gave consolidated guidance on the construction of MDR-TB regimens (26). They also advocated for a fully oral regimen to be used, with the injectable drugs only to be used where other options are not available or are exhausted (107). If an injectable drug is to be used, then amikacin is preferred as kanamycin and capreomycin are no longer recommended by WHO; injectable drugs should only be used if accompanied by monitoring for hearing loss. All three Group A agents (considered highly effective and strongly recommended unless contraindicated) and at least one Group B agent (conditionally recommended as agents of second choice) should be included to ensure that treatment starts with at least four TB agents that are likely to be effective. If only one or two Group A agents are used, both Group B agents are to be included. If the regimen cannot be constructed using agents from groups A and B alone, Group C agents are added. Data are lacking on the use of bedaquiline in children under 6 years and on the use of delamanid in children under 3 years (26).

Although the WHO-recommended duration of treatment is 18–20 months, WHO suggests that in children younger than 15 years with less severe disease, the duration of treatment could be shorter, as little as 9 months. Although delamanid and bedaquiline are often recommended for only six months, given that the original trials used that treatment duration, there is no evidence to suggest that longer regimens are harmful and, in many patients, longer durations are needed.

Box 3. Key elements for consideration in managing MDR/XDR-TB in children

You may wish to consult the Sentinel Project field guide *Management of multidrug-resistant tuberculosis in children* for further helpful and practical guidance on aspects of MDR/XDR-TB management in children and adolescents (28).

Management of MDR-TB disease

- Use an all oral regimen in most patients that includes all three Group A agents and at least one Group B agent, such that at least four likely effective drugs are included at the beginning of treatment. If only one or two Group A agents are used both Group B agents should be included in the regimen. Group C agents should be used when an effective regimen (four likely effective agents) cannot be designed with group A and B drugs.
- Prioritize group A and B drugs as well as delamanid in children over 3 years of age.
- A team approach in the clinical management of difficult-to-treat children and adolescents is recommended (TB Consilium or ptbnet) in order to benefit from the advice of experienced colleagues.
- Monitor closely for treatment response and drug adverse events.
- Follow the latest WHO recommendations on managing HIV coinfecting paediatric MDR-TB patients (108).

Table 1. Grouping of medicines recommended for use in MDR-TB regimens

Groups and steps	Medicine	
Group A Include all three medicines	Levofloxacin or moxifloxacin	Lfx Mfx
	Bedaquiline	Bdq
	Linezolid	Lzd
Group B Add one or both medicines	Clofazimine	Cfz
	Cycloserine or terizidone	Cs Trd
Group C Add to complete the regimen and when medicines from groups A and B cannot be used	Ethambutol	E
	Delamanid	Dlm
	Pyrazinamide	Z
	Imipenem-cilastatin or meropenem	Ipm-Cln Mpm
	Amikacin (or streptomycin)	Am (S)
	Ethionamide or prothionamide	Eto Pto
	<i>p</i> -aminosalicylic acid	PAS

In summary, in the context of suspected MDR-TB infection, the focus should be on obtaining patient specimens for bacterial confirmation via culture or molecular tests, in addition to a clinical history of exposure from a confirmed or suspected MDR-TB source case, in line with recent WHO recommendations. The history of exposure and symptoms are, however, more important to make a diagnosis, and immune tests (IGRA or TST) maybe helpful if positive. Treatment for MDR-TB infection in children and adolescents should be based on the best currently available scientific evidence, and is likely to involve a later generation fluoroquinolone alone or in combination with another drug to which the strain from the source case is susceptible. MDR-TB disease in children and adolescents can either be bacteriologically confirmed or clinically diagnosed. When designing a regimen for the treatment of MDR-TB in this group, decisions should be guided by DST on the isolate from the child/adolescent, or, if clinically diagnosed, by the pattern of resistance from the source case. Treatment should be based on updated guidelines and recommended regimens and doses. The use of an all oral (injectable free) regimen based on the WHO recommended anti-TB drugs, re-ordered in 2019, should be pursued.

10. Integration of TB prevention and care at primary care level

Children with TB often do not present to TB services as disease frequently manifests with non-specific, general symptoms. In many contexts there is a lack of awareness of childhood TB among child health providers in other health services to which children may present, commonly leading to misdiagnosis and delayed treatment initiation. Integration of TB services with other child health services, notably maternal and child health, is therefore a crucial strategy to improve prevention, diagnosis and treatment of childhood TB in endemic settings (43,44). Integration is required at the global level through increased intersectoral collaboration among United Nations agencies (34). On a national level, TB programmes need to work closely with other organizations that provide health-care services to children. Family-centred and community-based care models and strategies that are already established, such as Integrated Community Case Management (iCCM) or Integrated Management of Childhood Illness (IMCI), can be modified and used to raise the level of awareness of TB (109).

The 2016 United Nations Children's Fund (UNICEF) consultation on childhood TB integration, held in New York, represented an important step forward in addressing TB as part of a wider effort to end preventable childhood deaths. Its aim was to stimulate dialogue between traditional TB stakeholders and those that are instrumental in moving the childhood TB agenda forward but have not historically been actively involved in childhood TB (110). The key actions put forward by this consultation comprised increasing the visibility of childhood TB among the broader agenda of preventable childhood deaths, as well as harmonizing terms and definitions in order to assist integration through common understanding.

Children living in TB endemic areas often face multiple health challenges, such as coinfection with HIV and other pathogens, malnutrition and diarrhoea. Access to and quality of health care also varies considerably (111). Disease-specific vertical health programmes, like TB services, do not address the many other challenges that children with TB infection or disease have to deal with. Integrating TB services with other child health services such as antenatal care, HIV clinics, child health clinics, vaccination services or nutritional rehabilitation centres would help to increase the number of detected cases (112). Earlier detection and improved management of co-morbidities, such as HIV coinfection or malnutrition, could potentially improve treatment outcomes of TB disease (112). Further, integration of health services would increase the opportunities for prevention of all these diseases.

As an example, HIV is the strongest independent risk factor for progression of TB infection to TB disease, and TB is the main cause of death among HIV-infected patients (113). Accumulating evidence points to the benefits of integrated TB and HIV care, as well as other child health services (114). Historically, services for each of these diseases have been provided through vertical programmes dedicated to each disease and its prevention and care. Integrating these services has the advantage that care providers pay attention to prevention and care of both diseases and their common

risk factors. Implementing these services is complex and no blueprint exists as to which approach is best. In a previously proposed framework, implementation required functional integration at policy and budget level, clinical integration at primary health care level and organizational integration of resources and processes (115). Many gaps remain between established TB/HIV care integration policies and their implementation in dedicated primary health care clinics. One ongoing clinical trial investigates how integrated TB/HIV services in rural primary health care clinics are able to reduce mortality from both diseases (116). Findings from such trials are expected to provide further information on how to address current shortcomings of implementation of TB/HIV services.

Integration of TB prevention and care with other child health services is important in all regions of the world. Some aspects of TB service integration may however be more relevant to specific regions than others. For the WHO European Region, integrating TB services with more general child health services should have the highest priority. The current transition from vertical health-care models to more coordinated models with strengthened primary health care provides an opportunity to address the challenge of TB service integration (117). All stakeholders in child health should be sensitized to TB, and referral and financial reimbursement between the various services should be simplified. Special benefits to child health providers to work on the early detection of infectious diseases (including TB) can also be considered.

Supporting optimal treatment outcomes in children requires not only providing robust treatment regimens but also addressing the other economic, social and psychological needs of the child and their family (118). MDR-TB in a child usually signifies disease in other household members, and a family-centred approach to care needs to be utilized. Also, adherence support is crucial in MDR-TB. Paediatric patients are often grouped into a large category; however, approaches to optimizing adherence differ greatly depending on the age of the child. Whenever possible, children should be quickly reintegrated into their communities and usual activities, and as long as they are physically feeling well, they should not be excluded because of fears about contagion or transmission.

Lastly, it is important that equity, human rights and ethics principles are followed to guide the implementation of child and adolescent MDR-TB activities (119). Children are part of a family and are dependent on parents or primary caregivers for physical and emotional care and support. Health-care activities for children with TB should therefore be planned with the family, respecting each family's cultural background and particular strengths and needs. Parents should be encouraged and supported to stay with their child when they are receiving health care and to accompany and support their child during procedures. Parents should also receive all the information and support they need and request throughout the course of their child's or adolescent's treatment (120). Informed consent refers to the process of engaging parents as partners in the delivery of health services by giving them sufficient and relevant information to enable them to make decisions for their children. It is a basic

right and an important means of upholding a patient's autonomy. It is an ongoing and dynamic process that must be continually monitored and renewed during the whole time a patient is receiving care.

Apart from screening, diagnostics and treatment, children and their parents are in need of counselling and other forms of social support, such as health education, and psychological and material support. Child groups with special needs include orphans, street children, children of migrant populations and child-headed households; these children are particularly vulnerable and their vulnerability needs to be taken into consideration when making decisions regarding their care (119).

11. Vaccination

It remains irrefutable that an efficient vaccine would be one of the most cost-effective measures to control TB (121,122). Vaccination with BCG at birth for infants who are at risk or those living in high-incidence settings is one of the key components of WHO's End TB Strategy and protects from the more severe forms of TB (123). Several BCG vaccine substrains are available globally and although unquestionably safe, after several billions of doses administered, efficacy remains debated (124). In the WHO European Region as a whole, the most commonly used BCG vaccine substrain is BCG Denmark, produced at the Statens Serum Institut in Copenhagen, Denmark (125); while, in high-incidence eastern European countries and former Soviet states, the predominant substrain used is BCG Moscow (122).

Although some BCG substrains are reported to be more reactogenic than others (126–128), a recent systematic review concluded that substrain variation is not responsible for differences in protection (60). Worldwide, it seems that the level of protection conferred by BCG differs between studies and populations analysed; the systematic review of randomized controlled trials on BCG found that absence of prior exposure to *M. tuberculosis* or environmental mycobacteria was associated with enhanced protection (60). Among vaccinated neonates, protection against pulmonary TB was 59%, and among children BCG protected at a level of 74%.

Another study systematically reviewed and analysed available data on the time span of BCG-mediated protection (129). Here, efficacy ranged from 44% to 99% in 11 studies investigated with evidence that protection can last up to 10 years, while another study showed no protection at all. The authors confirmed that protection varies across populations to a degree that cannot be attributed to chance alone. Recently, characterization of the T-cell populations present in BCG-vaccinated children demonstrated waning central memory immunity over time, which may support booster vaccinations (130). However, BCG revaccination is not recommended by WHO (61).

Measuring prevention of infection by interferon- γ release assay conversion rather than prevention of disease is an alternative approach to evaluate vaccine efficacy. Roy et al. (2014) found 18% efficacy of BCG compared to unvaccinated controls in preventing infection in vaccinated children through analysis of 14 studies (131).

BCG is also known to provide protection not only against TB but also towards other pathogens and diseases not related to TB; this is known as the non-specific effect. It is perhaps not surprising that BCG could provide protection against leprosy and severe forms of Buruli ulcer, caused by *Mycobacterium leprae* and *Mycobacterium ulcerans*, respectively (132,133). However, BCG is also demonstrated to have a beneficial effect on reducing all-cause mortality in infants (134). Trained

innate immunity is considered to be the main mechanism behind the non-specific protective effect of BCG (135). The WHO recommended BCG vaccination strategy is summarized in Box 4.

Despite the extensive work which has been conducted to decipher the BCG mechanism of action, new TB vaccines are still needed as BCG only provides partial protection worldwide and BCG revaccination is not recommended despite positive results in a recent phase II trial (136). In the past two decades, considerable progress has been observed in the development of novel vaccines against TB. From a vaccine pipeline that was practically empty of candidates prior to 2000, 13 TB vaccine candidates are currently in the clinical trial pipeline and dozens more in preclinical development (137). The pathway of licensure for a vaccine candidate could take up to two decades from discovery. The sheer quantity of participants needed to constitute meaningful numbers of TB cases in an efficacy trial indicates the huge financial investment required for advanced clinical testing of novel TB vaccines. The length and cost of clinical trials have emphasized the need for a correlate of immunity following vaccination which could identify promising candidates in early pre-clinical or clinical development. Introduction of new vaccines is essential by 2025 if the WHO End TB targets are to be achieved by 2035.

Box 4. WHO position on BCG vaccination (61)

A single dose of BCG is recommended to be given to all healthy neonates at birth or at the earliest opportunity thereafter in all countries with high-incidence of TB. In low-incidence countries, selective vaccination is recommended of:

- neonates born to parents with current or previous TB;
- neonates born in households with contacts to high-incidence countries and/or high leprosy burden;
- neonates in any other locally identified risk group with TB and/or leprosy disease.

WHO recommends vaccination of special populations and notes certain contraindications.

- BCG is not recommended during pregnancy.
- BCG is contraindicated in people with severe immune suppression.
- Children with HIV who are clinically well and immunologically stable should be vaccinated with BCG.
- 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.

BCG vaccination of older age groups is recommended for the following:

- unvaccinated TST- or IGRA-negative older children, adolescents and adults from settings with high incidence of TB and/or high leprosy burden;
- unvaccinated TST- or IGRA-negative older children, adolescents and adults moving from low to high TB incidence/leprosy burden settings;
- unvaccinated TST- or IGRA-negative people at risk of occupational exposure in low and high TB incidence areas (e.g. health-care workers, laboratory workers, medical students, prison workers, other individuals with occupational exposure).

Revaccination is not recommended, but is under evaluation in clinical trials.

12. Conclusions and vision

This regional guidance intends to inform all stakeholders involved in DR-TB prevention and care in children and adolescents. A wide array of helpful guidance documents are now available for clinicians managing children and adolescents exposed to DR-TB or sick with DR-TB disease. These include field guides with practical, hands-on information. As evidence-based guidance, this publication requires regular updating, in line with the newest emerging evidence and knowledge. Childhood and adolescent TB, both drug-susceptible and drug-resistant, need to be further prioritized in the regional response to this major public health threat. TB elimination, as set out both by the Sustainable Development Goals and End TB Strategy, will only be feasible with dedicated strategies aimed at the young. Further research into new drugs and randomized clinical trials will guide the most effective treatment regimens. The injectable-free MDR-TB regimens recommended are a first step towards more bearable and tolerable treatment. An improved vaccine will be the most effective means of helping prevent further infection and disease among children and adolescents. However, wide implementation of BCG, a safe but only partially effective vaccine, remains important to reduce disseminated disease in young children. Lastly, further integration of TB prevention and care for the young with primary health care and other infectious diseases services is warranted to raise awareness of the interconnectedness of all areas of child health and notably infectious disease. Achieving integrated health services will significantly aid national TB programmes to meet the fundamental challenges they are facing today.

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