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Regional workshop on child and adolescent Tuberculosis in the WHO European Region

4–5 December 2017, Copenhagen, Denmark

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Abstract

Against the backdrop of widespread tuberculosis (TB) among vulnerable and marginalized populations, including children and adolescents, and in the context of increasing complexities resulting from HIV coinfection and multidrug-resistant TB, the WHO Regional Office for Europe convened a workshop of key experts working in the field of both TB and paediatric specialities in the WHO European Region on 4–5 December 2017. Key issues such as missed cases of TB among this age group, the threat of multidrug-resistant TB transmission and the availability of child-friendly formulations were discussed at length and practices and experiences were shared. This report summarizes the keynote presentations and ensuing interactions among participants, the poster sessions, and the panel and group discussions.

Keywords

Tuberculosis - diagnosis, drug therapy, prevention and control
Tuberculosis, Multidrug-Resistant - diagnosis, drug therapy, prevention and control
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Abbreviations

BCG	bacille Calmette–Guérin
DR-TB	drug-resistant tuberculosis
DS-TB	drug-susceptible tuberculosis
DST	drug-susceptibility test
ECDC	European Centre for Disease Prevention and Control
EEA	European Economic Area
EECA	eastern Europe and central Asia
ERI-TB	European Tuberculosis Research Initiative
EU	European Union
FDC	fixed-dose combination
GDF	Global Drug Facility
IGRA	interferon gamma release assay
IMCI	Integrated Management of Childhood Illness
LTBI	latent tuberculosis infection
MDR-TB	multidrug-resistant tuberculosis
RR-TB	rifampicin-resistant tuberculosis
TB	tuberculosis
UN	United Nations
UNICEF	United Nations Children's Fund
USAID	United States Agency for International Development
XDR-TB	extensively drug-resistant tuberculosis

Executive summary

After decades of relative neglect, the tuberculosis (TB) epidemic in children[1] is back in the spotlight. The goal of zero TB deaths in children has been endorsed by the international TB community and key stakeholders have united in their efforts to make this goal a reality.

Childhood TB can only be effectively addressed by collaboration across health systems and communities, and it is critical that childhood TB is prioritized in national health strategies, plans and budgets. It is also crucially important that childhood TB services are well integrated within national health systems, embracing primary health care, paediatric and maternal care services and other mother and child health initiatives. TB is difficult to diagnose in young children and may remain dormant and undetected until the onset of serious and life-threatening forms of the disease. Vigilance and early diagnosis are essential to prevent unnecessary suffering and improve treatment outcomes. On the other hand, TB in adolescents has additional challenges because this age group is more prone to the effects of social marginalization, stigma and discrimination. Unnecessary and prolonged hospitalization during the pre-adult stage of life has long-lasting consequences for educational attainment, employment opportunities and marriage prospects. This age group is also more likely to suffer from psychological as well as physical consequences of the disease, and some adolescents can also start to exhibit adult behaviour such as alcohol abuse and smoking. Thus, treatment services must recognize and be attuned to the unique needs of this age group.

The Regional Workshop on Child and Adolescent Tuberculosis in the WHO European Region took place in Copenhagen, Denmark on the 4–5 December 2017 and brought together country representatives and experts from 35 countries or territories of the Region, representatives of international partners (European Centre for Disease Prevention and Control (ECDC), the Global Fund to Fight AIDS, Tuberculosis and Malaria (Global Fund), United Nations Children's Fund (UNICEF), the KNCV TB Foundation, the Global Drug Facility and the Global TB Caucus) and colleagues from the WHO Global TB Programme in Geneva. Progress made since the previous regional childhood TB meeting held in November 2015 and major challenges across a range of highly relevant topics in paediatric TB were openly debated at the poster sessions and group discussions. Important updates were given on new developments in the diagnosis and treatment of childhood TB and on the introduction of child-friendly dosages and fixed-dose combinations (FDCs) in the Region. Participants also engaged in group work to identify priorities for action to strengthen national polices.

The objectives of the two-day workshop were to:

- review country policies and practices in the prevention, control and care of TB and TB/HIV among children and adolescents;
- share country experiences, lessons learned and good practices;
- highlight the challenges of including childhood TB in national strategic plans in the era of the post-2015 global End TB Strategy and the TB action plan for the WHO European Region 2016–2020; and
- formulate a set of next steps to effectively update (if necessary) national policies and guidelines in line with WHO recommendations.

[1] All references to "TB in children" in this document include TB in both children and adolescents.

The expected outcomes from the workshop were that:

- participants should be updated on key changes to and aspects of the management and treatment of childhood TB;
- a set of priorities for childhood TB at country level should be developed/drafted; and
- the next steps in updating elements of current national strategic plans relevant to childhood TB should be defined in line with the global End TB Strategy and the TB action plan for the WHO European Region 2016–2020.

This report summarizes keynote presentations by distinguished experts, poster presentations from three selected Member States, and group and panel discussions by participants. The agenda of the meeting is included in Annex 1 and the participant list is included in Annex 2

Background

TB continues to be an important public health problem in the WHO European Region. Significant challenges such as widespread TB among vulnerable and marginalized populations (including children and adolescents), increasing HIV coinfection and high rates of multidrug-resistant TB (MDR-TB) are further hampering efforts to reach the strategic goal to End TB by 2035 and achieve the pre-elimination phase for TB in the Region.

The full scope of the global and regional problem of TB in children and adolescents is not fully known. At least 1 million children are estimated to suffer from TB each year. In 2015 alone, 170 000 children died from TB, with an additional 40 000 TB deaths among HIV-positive children, despite treatment of TB in this age group being highly effective and most children tolerating first-line drugs well. Preventive treatment is also effective in children exposed to TB and child-friendly FDCs are easy to administer and in accordance with WHO dosage recommendations.

The true extent of the child and adolescent TB burden in the Region is highly uncertain: differences in reporting standards among countries can reflect different demographics, different case-finding practices, and under/overdiagnosis or under/overreporting of childhood TB. An estimated 3–4% of all TB cases in the Region occur in children under 15 years of age.

Only one third of the estimated 31 000 TB cases in children in the Region were detected and reported in 2016, with 10 174 cases of TB in children reported in that year. Drug-susceptibility test (DST) results in the same year were only available for 10% of children younger than 15 years of age; of these, 54 cases (4.9%) found to be resistant to rifampicin. The MDR-TB rate in this age group was 4.9%; remarkably, this is lower than in the adult population, especially for high-priority countries. However, the reasons for this are still unclear and under discussion.

Specific challenges such as unnecessary hospitalization and high rates of drug-resistant TB (DR-TB) are confounding the outcomes that can be achieved by TB control programmes in countries. Although the overall capacity for diagnosing adult and paediatric forms of TB is improving in the Region, it is still less than optimal. In addition, WHO still lacks policy guidance on managing contacts exposed to MDR-TB and DR-TB. This has particular implications for high-priority countries, where the highest rates occur in members of the 25–44 year age group, who are very likely to have young families.

The TB action plan for the WHO European Region 2016–2020 was endorsed at the 65th session of the WHO Regional Committee for Europe in September 2015 and is aligned with Health 2020 (a European policy framework and strategy for the 21st century), the global End TB Strategy and Sustainable Development Goal 3 (Ensure healthy lives and promote well-being for all at all ages). The plan calls on Member States to work towards achieving universal access to treatment, ensure the introduction of new TB medicines (including for children) in accordance with the most recent WHO policy guidance, use first-line FDCs to treat both adults and children, and provide paediatric drug formulations for treating drug-sensitive tuberculosis (DS-TB).

To this end, Member States must continue to update, adapt and revisit their TB national strategic plans. This requires concerted efforts to effectively combat TB in children, one of the most vulnerable patient groups. Strong and well-defined collaboration at both international and national levels are important for reducing the TB burden and associated suffering in children and adolescents.

Day I. Monday, 4 December 2017

The chairpersons were Dr Martin van den Boom, Ms Oxana Domenti and Professor Walter Haas.

Opening remarks

Dr Masoud Dara, Coordinator, Communicable Diseases Programme Manager, Joint TB, HIV and Viral Hepatitis Programme, WHO Regional Office for Europe

Dr Masoud Dara opened the workshop by first welcoming all participants and inviting them to briefly introduce themselves and share their expectations of the meeting. He asserted the importance of listening to and discussing experiences of TB activities among different countries with different burdens of disease, while focusing on children and adolescents, an important vulnerable group. The problem of MDR-TB in this group needs special consideration. He believed the meeting would stimulate participants to learn from the challenges and opportunities faced by practitioners every day and would increase their knowledge about new modes of diagnosis and treatment. Finally he stressed the importance of eradicating TB among children and adolescents in eliminating TB in the WHO European Region.

Welcome

Dr Nedret Emiroglu, Director of Programme Management and Director of the Division of Health Emergencies and Communicable Diseases, WHO Regional Office for Europe

Dr Nedret Emiroglu welcomed all participants and thanked them for their contributions to this very important second meeting on TB in children and adolescents. She discussed the current integration of activities among disease-specific interventions for TB, HIV and hepatitis, which have common at-risk groups in the WHO European Region. The high burden of MDR-TB makes TB an important public health problem despite the fact that the fastest rate of decline in TB is occurring in the Region. The WHO Regional Office for Europe is fully committed to addressing childhood TB because it is estimated that only one third of cases in this group are ever diagnosed or reported. Global and regional initiatives are leading the engagement with sustainable development goals but political commitment must translate into resources if the goal of zero deaths among children is to be reached. The firm declaration from the recent ministerial conference on TB held in Moscow in November 2017 that specifically mentions vulnerable groups, adolescents and children is building momentum for stronger intersectoral collaboration in anticipation of the first United Nations (UN) General Assembly High-Level Meeting on TB in 2018. Dr Emiroglu thanked all international partners and their representatives and national counterparts from all countries involved for their participation and also acknowledged all WHO staff who have worked hard to make the meeting a success. She concluded by reiterating her full support and encouraging all participants to share their experiences in order to produce a set of concrete actions to strengthen national plans for detecting and managing of TB in children and adolescents.

Ms Oxana Domenti, Parliamentarian and Co-chair of the Europe and Central Asian Regional Branch, Global TB Caucus

Ms Oxana Domenti introduced the work of the Global TB Caucus that brings together 2500 members of parliament from 140 countries, all united by a shared commitment to fight TB. She welcomed this unique opportunity to join together and learn from presentations and discussions on this very important subject. Members of parliament are in the best position to advance the political will needed to address the social and economic determinants of TB; Ms Domenti stressed the important work of politicians who serve as TB champions in ensuring access to TB services while "leaving no one behind". TB in the young has been ignored and neglected for many years, and although the disease is today fully preventable and treatable over 1 million children and adolescents suffer from TB worldwide and more than 210 000 die from the disease every year. Ms Domenti said that this loss is "deplorable" and represents "eroded human capital". The Global TB Caucus is very well aware of its responsibilities and considers that although the aim of zero TB deaths in children is ambitious it is also realistic and should be achieved. Recognized barriers to achieving this include resistance to bacille Calmette–Guérin (BCG) vaccination by the parents of young children; small and unprofitable markets for paediatric drug formulations; and slow licencing of new drugs. MDR-TB is a serious concern in the WHO European Region, and inaction is projected to cost an estimated loss of 0.9% of gross domestic product. There is a strong need to improve service models and to address the specific needs of children and adolescents. Ms Domenti concluded by predicting that the recent ministerial TB conference held in Moscow and the first ever UN General Assembly High-Level Meeting (attended by heads of states) to be held in New York this year will raise the profile of TB and thus bring us closer to achieving the strategic goal to End TB.

Overview of implementation of the TB action plan for the WHO European Region 2016–2020, including content relevant to childhood and adolescent TB

Dr Masoud Dara, Coordinator, Communicable Diseases, Programme Manager, Joint TB, HIV and Viral Hepatitis Programme, WHO Regional Office for Europe

Dr Masoud Dara opened by thanking the United States Agency for International Development (USAID) and the German Government for their financial support for the workshop. He then presented an overview of the latest epidemiological trends (for 2016) in the WHO European Region that have yet to be published. Routine data collected by the WHO Regional Office for Europe showed that 91% of all deaths from TB (estimated total 26 000) and 85% of new and relapsed cases occurred in high-priority countries (estimated total 290 000, among which 34 000 are HIV positive). The estimated number of rifampicin-resistant TB (RR-TB) cases was 122 000, with 71 000 cases of MDR-TB. The average notification rate for the Region is 27.2 per 100 000 population, but the distribution is strikingly uneven: from 11.3 per 100 000 population in the European Union (EU)/European Economic Area (EEA) to 52.3 per 100 000 population in the 18 high-priority countries. Sustained efforts have led to an impressive decline in the mortality rate (by 8.3% per year) and a steady decline in incidence rates (by 5.0% per year) between 2012 and 2106. Although these positive trends exceed those reported by other regions, HIV infection is clearly a growing threat. In fact, mortality from TB among those infected with HIV has been steadily increasing (by 4.9% per year) and incidence rates have also increased (by 8.7% per year) in the same time period.

Children are still dying from TB: on average, 13 children die every day in the Region. A total of 1 million children (range 0.6–1.5 million) are suffering from TB worldwide, representing 10% of the

global burden of TB. Childhood forms of TB are estimated to represent 3% of all TB cases in the Region: 10 174 childhood cases of TB were reported in 2016 (out of an estimated total of 31 000 TB cases). There are concerns over the current situation in the Region because of clear signs of missing cases, underreporting and empirical treatment. It is estimated that only one third of childhood TB cases are being detected, and only 1113 (10.0%) of children aged under 15 years had DST results in 2016. Rifampicin resistance was detected in 54 cases (4.9%). This low level of resistance in children is in marked contrast to the high rates of MDR-TB in adults in the high-priority countries (18.3% of new cases and 48% of previously treated cases). This difference needs to be further investigated. On average, DST results were reported for only a third of new pulmonary TB cases in 2016 (adults and children). Although childhood forms of TB are difficult to diagnose and often cannot be confirmed bacteriologically, other factors responsible for the apparent differences in MDR-TB patterns in children might be lack of awareness, stigma, lack of infrastructure and technical capacity to obtain pathological samples, and even limited reporting standards. It is disconcerting that many children receive empirical treatment that is not guided by DSTs, especially in countries where resistance to one or more first-line drugs is highly likely. Dr Dara compared emerging trends in the estimated childhood TB detection rates globally and within the Region (global, 41%; WHO Regional Office for Europe, 33%; high-priority countries, 32%; non-high-priority countries, 40%). Despite the apparent uniformity, there is in fact marked diversity: some high-priority countries (e.g. Uzbekistan, Bulgaria, Tajikistan and Turkey, in diminishing order of magnitude) exceed the global TB detection rate, while others (e.g. Armenia, Ukraine and Belarus) have a much lower detection capacity. He also pointed out that the observed annual regional decline in TB is slower in children than in the adult population. He attributed this to higher birth rates among specific at-risk groups such as migrants and called for strengthened control efforts in these groups.

Much less structured data are available on the outcomes of contact-tracing investigations and latent TB infection (LTBI) in children. Of the 53 Member States, only 14 provide information on the disease status of children aged younger than 5 years and known to have had close contact with a confirmed pulmonary TB patient. It is estimated that around 14 000 children aged younger than 5 years have LTBI and only approximately 7400 (55%) have received preventive treatment. This level of coverage is one of the lowest in the world and is not sufficient to ensure the elimination of TB by 2035. Although there is some doubt on the effectiveness of isoniazid preventive therapy in countries with high drug resistance, this treatment should be offered if the source does not have documented resistance to isoniazid.

Positive trends in treatment outcomes in the Region represent a turning point: success rates have increased to 77% for new TB cases, 62% for TB/HIV coinfection cases and 55% for MDR-TB cohorts. Dr Dara also observed that despite the good outcomes seen for TB/HIV coinfected patients, late presentation is associated with a higher mortality risk. Furthermore, the treatment success rate among MDR-TB cohorts is not sufficient to halt disease transmission. Although treatment outcomes in children appear to be very good, this might be misleading if many children are missed or misdiagnosed.

In the second part of his presentation, Dr Dara gave an overview of the TB action plan for the WHO European Region 2016–2020 and an update of its implementation and key activities. The strengthened global and regional policies have achieved good results: in the past five years over 1 million TB patients were cured, about 200 000 cases of MDR-TB were averted, and more than 2.6 million lives were saved in the Region. The action plan has the following key strategic objectives: full scale-up of rapid diagnostic tests; rapid uptake of new medicines; increased patient-centred care; shorter and more effective treatment regimens; research into new rapid diagnostic tools; and intersectoral approaches

for addressing inequities. He described some features of the action plan that are more relevant in this context.

The new drugs bedaquiline and delamanid are still not recommended for children, but some countries have experience in using them under strict pharmacovigilance standards, and the results need to be shared and published. Médecins Sans Frontières has also done some very good work in countries in the Region on the use of a short-course regimen for treating MDR-TB and such intraregional collaborations are very important. The recent document, A people-centred model of TB care: blueprint for EECA countries on modified models of care, released as part of the TB Regional EECA Project (TB-REP), will enable countries to reorganize their health systems and provide more patient-centred care; however, experts in some countries maintain that children are best treated in hospitals. Another leading project, the Barcelona course on health financing for universal health coverage, is increasing the capacity to move towards patient-centred care in the Region. Moreover, an interregional workshop on refugees/migrants that took place in Catania in 2016 has led the way towards achieving a minimum package of health services for cross-border TB with the collaboration of countries from the Eastern Mediterranean Region. The European Tuberculosis Research Initiative (ERI-TB) and the Special Programme for Research and Training in Tropical Diseases (TDR) have initiated more collaborations designed to increase country-oriented and operational research.

The Regional Director for Europe, Ms Zsuzsanna Jakab, has been a strong advocate of tackling TB in children and adolescents, culminating in the recent Moscow Declaration to End TB, which features childhood TB very prominently. Other key activities were: contributing to scientific publications, the most recent being the analysis of MDR-TB surveillance data in collaboration with the ECDC and the KNCV TB Foundation; revising national strategic plans and updating clinical guidelines in Belarus, Kazakhstan, Kyrgyzstan, Slovakia, Tajikistan and Uzbekistan to include childhood TB; improving access to child-friendly dosages (i.e. of first-line FDCs) through collaboration with Global Drug Facility (GDF) and the regional Green Light Committee for the WHO European Region; improving data completeness on child and adolescent TB through standardized WHO TB data collection; assessing childhood TB during national TB reviews in Kazakhstan, Kyrgyzstan, the Netherlands, Slovakia, Tajikistan and Uzbekistan; and an ongoing survey on the status of national strategic plans and TB clinical guidelines.

Plans for activities in the immediate future have already been set: a compendium of good practices will be prepared ongoing support will be provided to countries on TB diagnosis, treatment and care with special focus on multidrug and extensively drug-resistant TB (M/XDR-TB) and TB/HIV coinfection. In addition, there will be close follow-up of the Moscow Declaration and a report will be submitted to the 68th session of the WHO Regional Committee for Europe. Preparations are also in full swing for the UN General Assembly High-Level Meeting on TB due to take place later in 2018.

Discussion points and comments

On concluding his presentation, Dr Dara asked audience members to respond to the recent observation that DST results suggest that in the WHO European Region children have much lower rates of RR-TB compared with adults. This unexpected and unexplained finding has not been observed in other regions.

Participants found this result surprising and some questioned whether all children are being tested, especially contacts of MDR-TB patients, and whether such data are being collected and reported. One participant suggested that high-priority countries might not be reporting. A representative from the

Russian Federation did not support this, and affirmed that high numbers of MDR-TB cases are being reported in young age groups in the Russian Federation. The same was stated by a Moldovan representative. Many agreed that only approximately 30% of children are likely to be culture positive and these cases are often are not diagnosed or confirmed bacteriologically. It was also pointed out that the literature suggests MDR-TB strains might be less infectious, and this possibility needs to be explored. It was also agreed that more comprehensive routine data need to be collected systematically for this age group using smaller age intervals, with raw data (not only proportions) being shared.

Dr Dara also asked participants to suggest possible reasons for the marked differences in childhood TB detection rates across countries and which factors have improved LTBI detection.

A participant from France reported that although 70% of adult patients are diagnosed through passive case-finding, 70% of children with TB are identified by contact tracing. This suggests that countries without good policies on contact tracing will miss many cases of childhood TB. It was generally agreed that preventive therapy is very important and that new regimens need to be agreed for contacts of MDR-TB patients. A participant from Bulgaria also shared the fact that in this country the number of MDR-TB cases in adults is reducing and that one person in the Ministry of Health is responsible for ensuring that all contacts of M/XDR-TB cases are traced and followed up. Only one child with MDR-TB has been diagnosed in the country in the last three years.

Poster sessions

Session chairs: Dr Martin van den Boom and Professor Walter Haas

Representatives from one low-burden country (the Netherlands) and two high-priority countries (Belarus and Kazakhstan) presented their national perspectives during this poster session.

Perspective from a low-burden country: the Netherlands

Dr Connie Erkens, General Secretary, Committee for Practical TB Control, KNCV TB Foundation

Epidemiology

Childhood TB is rare in the Netherlands. The reported incidence rate was 5.2 per 100 000 population in 2016 (aged under 18 years), with 56% having pulmonary forms of TB. Most cases were in foreign-born individuals (74%), and 5% of all notified TB cases were related to childhood forms of TB. In 2016, the absolute number of reported cases of childhood TB was small (18 cases in the 0–4 age group, 31 cases in the 5–14 age group, with no cases of MDR-TB reported). The incidence of TB in children and adolescents is very low among the Dutch-born population (1 per 100 000) and higher among the foreign-born population (10 per 100 000). The risk in the latter is estimated to be up to 20 times higher than in the former. No deaths were reported in this age group in the last five years, and only two cases of miliary TB were reported in 2016. In the same year, 80% of cases in the 0–4 years and 60% of cases in the 5–14 years age groups were detected through contact tracing.

Prevention policies

The Netherlands performs active case-finding among high-risk groups, including contacts of infectious cases, migrants and asylum seekers. Since 2015, LTBI screening of all new migrants aged under 18 years is conducted upon entry to the Netherlands and BCG vaccination has now been extended to infants aged under 1 month in high-risk groups (defined as having at least one parent born

in a country with an incidence of more than 50 per 100 000 population). Other groups routinely screened are people living with HIV and patients receiving immunosuppressive treatment, with a strong focus on children and young adults. A total of 1697 individuals with LTBI were reported in 2016 (of these, 182 were under 18 years old). Trend analysis has shown that LTBI is concentrated in the larger cities, along with a few hot spots where asylum seekers are screened and housed upon arrival. Contact tracing is based on the so-called "stone-in-the-pond approach" based on the proximity to the index case and which also prioritizes young child contacts. Contacts with MDR-TB are assessed clinically but no preventive treatment is given.

Diagnosis

The national diagnostic algorithm for managing patient contacts was updated in 2017; it stresses the importance of active case-finding. The algorithm recommends full diagnostic testing (including the Mantoux tuberculin skin test, chest X ray and bacteriological examination) for symptomatic groups. The cut-off point for the tuberculin skin test is an induration of 5 mm. Candidates with an induration of 5 mm or more undergo further screening by chest X ray, and those with a visible BCG scar are retested with the interferon gamma release assay (IGRA; e.g. T-SPOT TB test, QuantiFERON-TB Gold In-Tube test). Children and adolescents who meet the criteria for LTBI are offered preventive therapy in accordance with WHO guidelines.

Treatment policies

Treatment policies follow the recommended WHO guidelines. Child-friendly FDCs are not yet available in the Netherlands. Children are only hospitalized if clinically indicated. The preferred preventive therapy consists of a three-month regimen of isoniazid plus rifampicin, which has been found to be patient friendly, effective and safe. In total, 97% of children reported as having LTBI in 2016 started treatment and 93% completed treatment. There is no official policy on managing the contacts of MDR-TB cases: the national consilium reviews each case on an individual basis. No preventive treatment is routinely offered to this group in the Netherlands.

Monitoring and evaluation

Monitoring data are collected by TB control units of the Department of Public Health and referred to the National Institute for Public Health and the Environment (RIVM). The last review was conducted in 2013.

Human resource development

TB in children forms part of the postgraduate medical curriculum but is less represented in undergraduate medical training. TB nurses are the most important links between patients and their attending physicians, and a digital tool kit has been developed to further enable child-oriented TB treatment and care.

Country documents and governance

The national diagnostic algorithm for contact investigation in children was updated in 2017 and the latest national plan for 2016–2020 has one chapter dedicated to TB in children and adolescents.

Key challenges and future activities

- The quality of passive case-finding in a very low incidence setting needs constant communication and review among TB experts and with national paediatric groups and associations.
- Coverage of BCG vaccination in neonates needs to be improved in high-risk groups.

- LTBI management in asylum seekers younger than 18 years needs improvement. Treatment guidelines for LTBI need to be implemented more rigorously.
- Short-course rifapentine and isoniazid preventive treatment regimens need to be introduced.
- Introducing new paediatric formulations within the country is difficult because of the small number of cases. Stronger advocacy is needed to facilitate the availability of these drugs, as well as rifapentine, which is not available in the country.
- Stronger liaisons need to be formed with paediatric associations.

Perspective from a high-priority country: Belarus

Dr Alena Skrahina, Deputy Director for Scientific Work, State Institution, Republican Scientific Practical Centre for Pulmonology and Phthisiology

Epidemiology

Belarus is a high-priority country that is experiencing a positive trend (i.e. a steady decrease) in the number of MDR-TB cases. Adolescents in the 15- to 17-year age group have much higher MDR-TB rates than their younger counterparts, but numbers have been decreasing since the peak in 2015. There appear to be fewer TB cases in children compared with neighbouring countries; however, it is possible that not all cases are being detected or reported. MDR-TB cases have also been reported: in 2016, six children (under 14 years old) and 18 adolescents (15–17 years old) were found to have MDR-TB. No deaths were reported among the MDR-TB cohort in 2016.

Prevention policies

Mass screening of high-risk groups is performed every year but is no longer compulsory. Cases of TB among close contacts of infectious patients can be missed and underdetection is a challenge. High-risk groups include: close contacts; children who have not had BCG vaccination; HIV-positive and other immunocompromised children (e.g. those taking TNF-α inhibitors, after transplantation); children of parents who are alcoholic or drug abusers; refugees; children living in hostels and residential orphanages; and the disabled. Preferred testing methods are the Mantoux tuberculin skin test (for children aged under 7 years) and the Diaskintest (for older children and adolescents). Mandatory BCG vaccination was halted in 2016 and routine BCG vaccination is now offered in the first week after birth.

Diagnosis

Underdiagnosis of TB in this age group is presumed across the entire country despite the availability of a full range of diagnostic tools and procedures. Rapid molecular tests such as GeneXpert, line probe assays and DSTs for both first- and second-line drugs are available. Both the tuberculin skin test and the Diaskintest are used; the IGRA was registered in 2016 and is now more easily available. HIV testing is compulsory.

Treatment policies

National treatment guidelines are fully complaint with WHO guidelines and all measures are taken to ensure that the best treatment is offered to all children and adolescents. Although all TB drugs are available, paediatric formulations of FDCs are not yet available in the country. All treatment decisions for cases of MDR-TB in children and adolescents are made by the national consilium of TB experts, and 51 children and adolescents have received either bedaquiline or delamanid. The country has already gained practical experience of using bedaquiline in 16 children aged younger than 6 years (note that this is younger than the WHO age recommendation for use of this drug). Children can

receive treatment in hospital or sanatoria or can receive directly observed therapy at home. Educational and social support is also provided. Preventive treatment is offered to all children aged under 5 years if the source case is DS-TB. Children exposed to an infectious case of MDR-TB are not treated but are instead followed up regularly (for two years if the source case is cured, for five years if the source case dies).

Monitoring and evaluation

Epidemiological monitoring data are collected electronically and transmitted to a central unit. Each region is visited by a dedicated monitoring team twice yearly. The national TB programme was reviewed in 2015 and a technical and monitoring mission was held in August 2017.

Human resource development

There are 44 paediatricians in the country (1 per 20 000–22 000 children) and more specialized paediatricians are needed. TB specialists generally have a one-year internship at the Medical University or four months of training at the Belarus Medical Academy of Postgraduate Education. Refresher courses are also organized regularly.

Existing stakeholders

There have been close collaborations with a varied number of national (ministries of health, national TB programme managers, local nongovernmental organizations) and international partners (such as the Global Fund, Médecins Sans Frontières, Red Cross, WHO).

Country documents and governance

Six executive orders were issued between 2012–2017, covering a range of activities: clinical guidelines on the treatment of TB and its drug-resistant forms; TB control in outpatient health care organizations; laboratory diagnostics for TB; diagnosis, prevention and treatment of serious adverse reactions to the BCG vaccine; outbreaks of TB infection and contact tracing; and immunodiagnostics and chemoprophylaxis of TB among children.

Key challenges and future activities

- The high prevalence of TB and the high number of confirmed RR-TB and MDR-TB in the adult population is not being reflected in this young age group as only 0.6% of confirmed cases are found to have resistant strains. An estimated 69.7% of child contacts are exposed to MDR-TB but exact data on how many children eventually develop TB are still lacking and no preventive treatment is available.
- The incidence of BCG-associated osteitis and spondylitis is high (42% of the vaccinated cohort in 2015 and 32% in 2016). Molecular tests (line probe assays) to confirmed that the BCG strain was the cause of these complications.
- Contact tracing may not be sufficiently rigorous. Some parents hide their children from the contact-tracing service because of the associated stigma. Health care workers may also lack the extra motivation required to reach all family contacts.
- The national cut-off point used to interpret the tuberculin skin test (an induration of 5 mm) is not consistent with the WHO recommendation (≥10 mm) and the Diaskintest has not been approved or recommended by WHO.
- Very young children and adolescents up to the age of 18 years share the same health care services and are treated at the same hospital departments, and infection control measures may not be fully implemented in hospital settings. Despite repeated calls to reduce the length of hospitalization, progress is slow.
- Monitoring of active case-finding appears to be unnecessarily complicated or impractical.

Perspective from a high-priority country: Kazakhstan

Dr Kagaz Serikbayeva, Director, Department for Treatment of Children with TB and MDR-TB, National Scientific Center for Phthisiopulmonology, Kazakhstan

Epidemiology

Kazakhstan has made a lot of progress since the country's peak period of TB incidence from1997 to 2000. The main task now is to concentrate all efforts to improve the quality of services. The TB incidence rate has reduced by 33.0% in the 0–14 age group (to 6.6 per 100 000 population) and by 25.6% in adolescents (to 59.9 per 100 000 population) since 2014. These values are one tenth of the numbers recorded during the peak period; however, the number of MDR-TB cases in this age group is still high, especially in adolescents.

Prevention policies

At-risk groups among children and young adolescents have been revised in accordance with WHO guidelines. Standards were revised in legislation of 2015 and clinical protocols now include MDR-TB treatment for children and adolescents, dosing schedules for first-line drugs in children, and LTBI preventive treatment for immunosuppressed individuals. Mass BCG vaccination for neonates remains the national policy, and BCG vaccination is carried out in maternity hospitals one to four days after birth. Primary school pupils are revaccinated at age 6–7 years, and coverage of BCG vaccination is around 95%. Some parents refuse to have their children vaccinated (1.1% on average), and 12 cases of TB were reported in non-vaccinated children in the last 11 months. All close contacts are reviewed by TB specialists at polyclinics and TB dispensaries, and examinations are repeated after six months. Preventive treatment (six months of isoniazid or three months of isoniazid plus rifampicin) is provided for contacts and immunocompromised persons if there is evidence of LTBI. No treatment is offered to the contacts of MDR-TB patients.

Diagnosis

TB diagnosis in children remains difficult even though all modern diagnostic methods are available (e.g. BACTEC, GeneXpert, HAIN test) as well as other procedures such as gastric lavage, bronchoscopy and biopsy of affected extrapulmonary sites. Diaskintest is the preferred method for detecting TB infection and has been available throughout the country since 2015. The T-SPOT test (a commercial IGRA) is being registered for use in children with some form of immunodeficiency. TB diagnosis in children and adolescents is part of the national diagnostic algorithm adapted for TB care and follows WHO strategic recommendations.

Treatment policies

Children are treated according to WHO guidelines; treatment duration is 6–12 months for DS-TB cases. Cases of miliary TB or TB meningitis are treated for at least 12 months. A three-month course of rifampicin plus isoniazid is used as a preventive treatment. Combined drugs in FDCs are available for children weighing above 25 kg; a request for paediatric FDCs for those weighing less than 25 kg has been submitted, and it is anticipated that these will become available in 2018 thanks to the collaboration with the Global Fund. Most drugs are procured through the state budget and new anti-TB drugs are available thanks to donors. Hospitalization or admission to a sanatorium is still the mainstay of treatment, including preventive treatment, but the number of paediatric hospital TB beds has been reduced to 2500 nationwide and the length of hospital stay has also been reduced.

Monitoring and evaluation

All TB cases have been reported since 1997 and an electronic registry is now fully functional at all levels. Oblasts report quarterly to the central registry. The database now also includes all childhood forms of TB, as well as LTBI in children. Monitoring and evaluation of all TB control efforts includes regular site visits by a specially trained team that includes infectious disease and TB specialists, paediatricians, statisticians and representatives of consumer protection agencies. The Committee for Penitentiary Services also forms part of monitoring missions. All reports are overseen by the Ministry of Health of the Republic of Kazakhstan, which ascertains whether any recommendations from previous visits were implemented on time. The national TB control programme of Kazakhstan has been evaluated by WHO every year since 2012, with the last evaluation taking place in August 2017. TB in children and adolescents was last evaluated in February 2017.

Human resource development

Human resource development is ongoing, especially among medical staff; however, the recent introduction of postgraduate training courses in TB has not yet increased the number of doctors working in this field. TB in children and adolescents is included in the undergraduate and postgraduate medical education programmes of six higher education institutions.

Existing stakeholders

The Ministry of Health leads all TB control activity in the country and has collaborated with a number of educational institutions and international agencies such as the Global Fund, KNCV TB Foundation and Partners in Health. The Project Hope three-year programme "Addressing cross-border TB and TB/AIDS among labour migrants" that started in 2014 is an example of collaborative work with partners and stakeholders.

Country documents and governance

The comprehensive national action plan for 2014–2020, which has been approved by the Parliament of the Republic of Kazakhstan, now has a childhood TB component. All questions related to childhood TB are included in the Order of the Ministry of Health, Instructions for the organization and implementation of preventive measures for tuberculosis. TB in children and adolescents was included in the latest concept note to the Global Fund with the aim of obtaining new paediatric FDCs. As yet, there is no fixed plan to ensure universal access to quality drugs, but all first- and second-line drugs for adults are available in the country.

Key challenges and future activities

- Shortages of BCG vaccines have been experienced and an increased numbers of cases and deaths in the non-vaccinated child cohort have been observed. In the past, a high proportion of complications following BCG vaccination was a challenge (enlarged lymph nodes were most common, with one case of disseminated BCG); however, since shifting to the Japanese strain, the complication rate has reduced to around 0.02%.
- More specialized staff are needed to manage TB in this age group, but new workers are not motivated to work in this field.
- There are no clear guidelines for managing asymptomatic contacts with clear evidence of LTBI after exposure to an infectious source of MDR-TB.
- Some children have MDR-TB strains and the new drugs bedaquiline and delamanid may be their only option; however, these are not registered and are not available in the country. In addition, no anti-TB drugs with infant dosages are registered, including new FDCs.
- There is anecdotal evidence from a pilot project that children treated as outpatients (i.e. not hospitalized) discontinued treatment in higher numbers than expected.

- IGRAs (i.e. QuantiFERON-TB Gold In-Tube tests, T-SPOT TB test) are not yet available for detecting LTBI in immunocompromised individuals.
- There are plans to merge some hospital facilities treating childhood TB into fewer integrated units in the northern regions of the country with lower TB rates, while ensuring that access to treatment is not denied to families who may need to travel long distances. Efforts are under way to increase the numbers of fully trained staff to support TB children and adolescents receiving treatment (and even preventive treatment) as outpatients. Such services would cover financial, social and educational support, in addition to supervising therapy.
- Paediatric TB specialists for children aged under 6 years and specialist TB general practitioners for older children and adolescents will be trained through a special TB curriculum that is being introduced as part of the postgraduate medical training.
- A concept note has been sent to the Global Fund as part of the planned procurement of child-friendly FDCs for treating DS-TB in children throughout the country. These formulations are still not registered and will be imported under the category of humanitarian aid.
- Revision of BCG revaccination policies is due at the level of the National Advisory Committee on Immunization for the Ministry of Health.
- It is hoped that children and adolescents will have access to outpatient services and those suffering from MDR-TB can also receive treatment regimens that include new drugs.
- Introduction of IGRAs (e.g. the T-SPOT TB test) needs to be considered for HIV-infected TB patients (at least).

Discussion points and comments

Reactions to the three poster presentations and the ensuing discussion and comments are summarized below.

Insufficient case-finding and reporting. These are the biggest hurdles in diagnosing TB in this young age group; as stated by a participant, "nobody really knows how many children have TB in the Region". Integrated approaches that include antenatal care, maternal and child health clinics, adolescent health clinics and HIV clinics can improve this situation. Most affected children are discovered by active case-finding during contact investigations but good results depend on the motivation of health care workers leading these investigations as well as the full cooperation of patients and their families. The investigating team must be fully trained and strive hard to obtain the trust of index patients. However, this may not be easy, especially if other cultural or social barriers are at play.

BCG vaccination and associated complications. WHO has only recently reviewed the evidence on BCG vaccination in babies and will issue new guidelines in 2018 stating that BCG can be administered as soon as possible after birth. BCG complications are associated with vaccine quality, and some strains may be associated with higher complications in some countries. BCG vaccination polices in low-burden countries, many of which have discontinued mass BCG vaccination of children, are based on a balance between protection and the risk of complications from the vaccine. The estimated protective effect of the vaccine (50–80%) lasts for about 10 years.

Administration of preventive treatment. TB nurses in the Netherlands perform individual risk assessments; preventive therapy can then be administered by the parents or guardian, if they are deemed reliable. TB nurses monitor closely the therapy and can also provide directly

observed therapy if necessary. Resources for such extensive practices may not always be available in all countries.

Annual screening of children in high-priority countries. This is very resource intensive and the evidence of its effectiveness is limited. Some countries (e.g. Belarus) are working towards a more streamlined approach.

Methods used to detect LTBI. The Diaskintest is used in many countries in eastern Europe and central Asia (EECA) but is not recommended by WHO. Despite this, according to some participants, there is evidence in the Russian scientific literature that this test has results comparable to other tests such as the Mantoux tuberculin skin test and the QuantiFERON-TB test.

Low TB rates of TB in children aged under 5 years in high-priority countries. Some participants from low-burden countries found this surprising. No specific explanations were provided for this, but some participants suggested that high coverage of BCG vaccination (95%) could be a factor.

Limited availability of child-friendly formulations and new TB drugs. All participants shared concerns in this area. The lack of availability of the new drug rifapentine was used as an example by low-burden EU countries. The limited availability of FDCs for first-line drugs and the new drugs bedaquiline and delamanid was raised by high-burden countries. The low profit margin is an important barrier because it represents a strong signal to the private sector not to enter that market. This issue needs to be brought to the attention of politicians, and the Global TB Caucus is well placed to inform the appropriate politicians in all countries.

Stigma. Stigma is difficult to overcome and remains entrenched in the legal frameworks in many high-burden countries, forcing affected adults out of work and children out of school. This can contribute to poverty and suboptimal education and has a direct bearing on the social determinants of TB in the Region. Many societies fear contamination and are not ready to accept TB patients, despite widespread efforts to increase TB awareness and health literacy. Recent studies using the latest genetic methods have found no evidence that TB can be transmitted by patients undergoing treatment as they perform their normal daily activities. WHO is also currently preparing new evidence-based guidelines on infection control that support this position.

Protecting children's rights. Children and adolescents with TB may suffer abuse of their rights, including the right not to be discriminated against, the right to see their parents, the right to live in a supportive environment and the right to receive a normal education. A targeted approach among political and professional communities is being used by the Global TB Caucus to hasten the pace of implementing patient-centred models of care in the Region. Several high-priority countries are moving in the right direction and are implementing measures to guarantee these rights by reducing the practice of referring children to TB sanatoria and giving more support during ambulatory care.

Global TB Caucus

Ms Rosanna Flurry, Parliamentarian and Regional Director for Europe and Central Asia, Global TB Caucus

Strong political will is needed to overcome stigma and legislate to bring about the changes needed for countries in the WHO European Region to provide quality patient-centred care and provide treatment services close to patients' homes. The Global TB Caucus in the Region, led by Ms Oxana Domenti, has the support of 300 parliamentarians. This is the largest Global TB Caucus group so far and it is committed to working closely with civil society groups across the Region. TB in children has been neglected and the Global TB Caucus is keen to raise this issue to increase political support and obtain better funding to lead the response. Members and national working groups are pushing hard on many fronts including amending legislation, promoting strategic funding, increasing access to patient-centred care, adopting WHO guidelines and addressing social stigma. The Global TB Caucus was represented in a meeting in Moscow in November 2017, and is advocating for strong commitment to address childhood TB from all heads of state be attending the 2018 UN General Assembly High-Level Meeting on TB, due to take place in New York.

Introduction of child-friendly TB dosages and drugs into the WHO European Region

Dr Maya Kavtaradze, Regional Technical Advisor for Europe, Stop TB Partnership, GDF

Dr Kavtaradze gave a brief overview of GDF activities along with practical suggestions for participants to consider. GDF is hosted by the UN Office for Project Services and its strategic objectives focus on using market intelligence to strengthen procurement and global supply systems to facilitate the uptake of new drugs and new TB tools. It recently led the introduction of new paediatric drug formulations through providing technical assistance and grants. The first new optimized first-line FDCs as paediatric formulations became available worldwide through the GDF in 2016. These include RHZ 75/50/150 (75 mg rifampicin/50 mg isoniazid/150 mg pyrazinamide; dispersible tablets) and RH 75/50 (75 mg rifampicin/50 mg isoniazid; dispersible tablets). The first-line drug ethambutol (100 mg; film-coated tablets) and isoniazid (100 mg; uncoated tablets) are also available in paediatric doses. Child-friendly second-line drugs will become available from 2018. Child-friendly formulations are dispersible in water, have a good flavour and follow appropriate dosages by weight band. Approximately 75 countries have ordered paediatric first-line FDCs to date and several countries in the WHO European Region (Georgia, Kazakhstan, Kyrgyzstan, Tajikistan, Uzbekistan) and Kosovo (in accordance with Security Council resolution 1244 (1999)) have already received these drugs or have orders pending (Republic of Moldova, Ukraine). She observed that such orders dropped in 2015 and 2016, possibly because of suboptimal order management, but increased in 2017.

The new drug rifapentine (150 mg) is also available through the GDF and is being increasingly used to treat LTBI. It is now included in the WHO essential treatment list for TB drugs. She added that Estonia has used this drug in adults but no country has yet ordered this drug for use in children. Tajikistan was the first Member State in the Region to introduce the new paediatric formulations and all eligible patients in the country have received these drugs since August 2017.

As new child-friendly second-line TB drug formulations will be available as from 2018, Dr Kavtaradze anticipated that quantifying the exact amounts needed will be a challenge because it is difficult to predict the number of children who will require treatment. Drugs in this group include cycloserine (125 mg tablets), ethionamide (125 mg tablets), levofloxacin (100 mg tablets), moxifloxacin (100 mg tablets) and pyrazinamide (150 mg tablets). It is estimated that only around 1000 children in the Region will require DR-TB treatment. Thus, the small size of this market reduces the profit margin that finances further innovation in this area. She also reminded the audience that child formulations are set according to weight bands. Thus, the weight of the child is an additional detail that must be included the procurement order.

According to Dr Kavtaradze, a number of challenges need to be overcome so that children and adolescents to receive quality-assured medicines. Many countries in the Region, including the low-burden countries, still use crushed adult formulations for children because the focus remains on procuring drug treatments for adult patients. The quality of imported drugs that are not procured through the GDF (because of price differences) may be doubtful. A lack of awareness persists among medical professionals on the correct dosing schedule for first-line FDCs for children and many countries have not updated their treatment protocols. She also reminded participants that none of the countries in the Region are currently eligible to obtain first-line drugs through the Global Fund; however, rigid national regulations are still hampering procurement even where public funds have been allocated. In addition, very few countries have added paediatric formulations to their national essential medicine list and very often manufactures are not interested in bidding for such small quantities. Pooled procurement may help to resolve this problem. She warned that some wastage can be expected for procured first-line FDCs, as well as for second-line paediatric formulations, because it is difficult to accurately quantify the stocks needed. It may even be possible to negotiate with the Global Fund to minimize write-offs. Some technical assistance is available to high-priority countries in the introduction of new drugs through the GDF and USAID-funded projects, and the GDF also provides assistance with capacity-building to help with stock quantification and supply planning.

She concluded that GDF is committed to ensuring that all children receive the correct and best treatment, but this depends on the full cooperation and coordination of the national counterparts. The GDF is available to assist countries that may still have funding gaps.

Discussion points and comments

Treating young infants. The recommended volume of water to disperse these drugs is 50 ml. The advice of a paediatrician is necessary if the child is under 6 months old.

Countries must initiate registration. Many countries can import new TB drug formulations even if they are not locally registered through one-time waivers or other exceptions. The country has to be the party to initiate the registration process and must also include the drug/s in the national essential medicine list. The GDF will then help with the next steps by coordinating with manufactures. This applies to both high-burden and low-burden (e.g. EU) countries. None of the new paediatric formulations are patented so the issue of imported generic drugs does not arise. To date, only Turkmenistan has registered all TB drugs.

Procurement through the GDF. Many countries, especially high-income countries, are not aware that TB drugs can be procured from the GDF. The prices are the same for all countries (except for bedaquiline and delamanid) but some countries may qualify for Global Fund support if they meet eligibility criteria. Individual patients cannot procure drugs from the GDF. The drug catalogue and a detailed explanation of procurement procedures are available on the Stop TB website.

ERI-TB

Dr Andrei Dadu, Medical Officer, Joint Tuberculosis, HIV and Viral Hepatitis Programme, WHO Regional Office for Europe

A brief overview of the activities of ERI-TB since its launch in November 2016 was presented by Dr Dadu. The initiative aims to catalyse research in the WHO European Region to tackle the challenges that may halt progress towards achieving the 2035 targets of the End TB Strategy. Modelling current trends indicates that the current decline in annual TB rates in the Region can be accelerated with universal health care and by scaling up new rapid diagnostic tools, drugs and regimes; however, most countries will not achieve the pre-elimination phase of 10 new cases per 100 000 population by 2035. Research and innovation make up the third pillar of the global Stop TB action plan, as well as the TB action plan for the WHO European Region 2016–2020, and it is clear that new evidence-based interventions and faster advances in basic sciences must lead the way to achieving this goal. The speaker described the 15 members of the ERI-TB core group as experts who are currently working in the Region and added that the secretariat is actively seeking to expand the ERI-TB network. Discussions were initiated earlier in 2017 year by the ERI-TB secretariat at WHO to increase collaboration with the Structured Operational Research and Training Initiative (SORT IT) platform, which operates under the umbrella of the Special Programme for Research and Training in Tropical Diseases and is funded by several UN agencies. The European TB Research Initiative core group, together with its secretariat, recently launched a Region-wide online public consultation that included various stakeholders and partners in an attempt to define and prioritize TB research in the Region. Respondents from 39 Member States provided input and the results are being processed and analysed.

Update on new developments in the diagnosis and treatment of childhood TB and global perspectives on childhood TB

Ms Annemieke Brands, Technical Officer, Global TB Programme, WHO

Ms Brands opened her session by briefly presenting the global perspective on childhood TB. She again stated that more than 1 million children are suffering from TB and that 10–11% of TB cases each year are in children younger than 15 years. Children are dying from TB at a rate of 700 per day (total of 253 000 deaths in 2016, including children who are also infected with HIV). It is estimated that 25 000 children will develop MDR-TB each year and over 67 million children and adolescents are already infected with TB. The risk factors for TB and MDR-TB in children and adolescents are well known and include close contact with an infectious source of pulmonary TB, age younger than 5 years, severe malnutrition and immunodeficiency (including immunodeficiency related to HIV infection). She also remarked that the adolescent age group reported by the Global TB Programme (10–19 years) does not fit with the age classifications for children and young adults used in WHO surveillance and monitoring reports (0–4, 5-14, 15-24).

From a more regional perspective, Ms Brands stated that an estimated 31 000 (range 22 000–41 000) children have TB in the WHO European Region. A detailed analysis of the estimated versus actual numbers of reported cases revealed that only 40% of all affected children are being diagnosed and reported and that cases are being missed in all the countries in the Region. She stressed that children are also dying from TB in this Region and that an estimated 50% of infected children have access to or receive preventive treatment. Late diagnosis and lack of reporting for childhood TB are causing a

number of so-called practice gaps in the patient–provider pathway. Comorbidities such as pneumonia and undernutrition also make diagnosis more difficult. Very often, the diagnosis is made only higher (i.e. tertiary) level health care services, with severe pneumonia or severe malnutrition as the first presenting condition. Ms Brands strongly recommended the use of GeneXpert to diagnose MDR-TB and TB/HIV in children and also conditionally recommended the test for all cases of suspected TB in children. A meta-analysis of 15 studies found that Xpert MTB/RIF was 40% more sensitive than smear microscopy in children (specificity 98%, sensitivity well over 60%) compared with conventional culture methods (e.g. sputum induction or gastric lavage). She stressed, however, that a negative result does not rule out a diagnosis of TB. The next-generation Xpert MTB/RIF Ultra cartridge has now been recommended by WHO, although the increased sensitivity comes at the price of a higher false positive rate.

Childhood TB is a clear sign of ongoing transmission and Ms Brands highlighted the important challenges that must be addressed. Some are unique to the Region, such as: many missed cases; a high MDR-TB rate in children; interrupted access to drugs; limited availability of rapid drug sensitivity testing for first- and second-line drugs in peripheral areas; policies that focus on revaccination instead of providing preventive treatment; and vertical and insufficiently integrated health systems. She acknowledged that important achievements have been made in the Region: the treatment success rate in this group is over 85% and many Member States are orienting their policies, guidelines and funding to meet the needs of affected children. The response to childhood TB must now be scaled up to follow the current fast pace of annual decline in the population, and this could lead to the eradication of TB from the Region. Actions should include: active case-finding, with contact tracing initiated by the physician caring for the adult infectious source; maintaining clinical expertise so that cases can be confidently diagnosed in the absence of supporting microbiological confirmation; ensuring access to preventive therapy; and integrating and harmonizing LTBI management in children. She highlighted the fact that WHO has signed a new agreement for catalytic funding with the Global Fund that will focus on missed cases in 13 countries in the next three years. She announced that a USAID grant is leading new research in Africa into new models of care and a new diagnostic package. Furthermore, WHO will issue renewed guidelines on LTBI management, and the Roadmap for childhood TB (first published in 2013) will be updated in 2108.

Ms Brands ended her presentation by making a call for evidence-based approaches to care and for more research into basic sciences because a child-friendly point-of-care diagnostic test would be a game changer.

Day II. Tuesday, 5 December 2017

Chairpersons during the morning sessions of Day II were Dr Martin van den Boom, and Dr Alena Skrahina.

Chairpersons during the afternoon sessions were Dr Martin van den Boom, Ms Annemieke Brands and Ms Iveta Ozere.

Brief overview of contributions from the European working/task force group on childhood TB and update on an exchange with another WHO region

Dr Martin van den Boom

The Child and Adolescent TB Working Group is part of the Stop TB Partnership, the secretariat of which is hosted by the Global TB Programme of the WHO Regional Office for Europe in Geneva. Members of the Partnership are from all WHO regions and include paediatricians, academics, public health specialists, national TB programme managers, nurses and community representatives. A number of European scientific partners are also represented, including the European Respiratory Society, the ECDC and the KNCV TB Foundation. Dr van den Boom represented the European arm of the group in the recent annual meeting that took place in Kigali, Rwanda. The group meets regularly and has made key scientific contributions. Members reviewed more than 20 international publications and books in 2016 and 2017, the most recent of which is a global meta-analysis of MDR-TB treatment outcomes that is about to be published. Regional surveys of policy, practice and treatment guidelines for childhood TB in the Region have led to key programmatic contributions such as extensive updates of national clinical guidelines for childhood TB, childhood TB being reflected more strongly in strategic plans, and technical assistance in developing concept notes for grant applications to the Global Fund. In conclusion, the regional childhood TB working group has improved the coordination of childhood TB policies in the Region and has been a strong driver in increasing awareness and advocacy for children affected by this disease.

Integration of primary health care services for childhood TB

Dr Martin Weber, Programme Manager, Child and Adolescent Health, WHO Regional Office for Europe

Dr Weber started his presentation with an anecdote: he recounted how senior physicians in the past used to dismiss childhood TB as “not a public health problem” because “children are not infectious”. Since then, the care of children, especially of children with TB, has come a long way and an Integrated Management of Childhood Illness (IMCI) strategy has been adopted to reduce deaths and disability in young children. This is as a holistic approach consisting of both preventive and curative interventions that are evidence based as opposed to eminence based. It includes a set of treatment guidelines for primary care that addresses health systems issues associated with child care and prompts the timely referral of severely sick children to hospital. In EECA countries, IMCI guidelines are especially useful to prevent the widespread use of polypharmacy encountered in children receiving excessive (e.g. multiple antibiotics at the same time) or unnecessary (e.g. anticonvulsant therapy lasting many months to treat a single episode of febrile convulsions) medication.

According to Dr Weber, some unique features of childhood TB are shared by many high-burden countries in the WHO European Region. These include late diagnosis, despite the widespread availability of rapid diagnostic tests; suboptimal active case-finding because contact tracing is not extensive or systematic; many children being removed from their families and admitted to sanatoria, in some instances even for preventive treatment (constituting an infringement of their rights); and the use of non-evidence-based treatments such as hepatoprotector therapy.

The IMCI strategy uses a traffic light system to indicate the severity of the child's condition and the appropriate response. TB-related illness in children can present at one of three entry points: (i) acute, severe illness requiring urgent referral to hospital (e.g. cases of TB meningitis and military TB or severe fulminating pneumonia); (ii) a cough lasting more than 14 days and not responding to antibiotic treatment; or (iii) unexplained weight loss or malnutrition. A symptom-based pocket book for hospital care for children (available online or on mobile phone; also in Russian) has a section dedicated to TB which generally recommends that treatment guidelines follow national TB programme policies. The handbook is proving to be a very useful resource, especially for physicians in primary care, and a new edition with updated clinical guidelines will be published in 2018. Some countries in the Region (e.g. Armenia and Kyrgyzstan) are also producing their own adapted versions. He concluded by emphasizing the need for strengthened, integrated child health and TB programmes in the Region to reduce unnecessary hospitalization and give more support to affected children and their families.

Discussion points and comments

Ambulatory care. Unnecessary hospitalization remains widespread in many parts of the Region and strenuous efforts are under way to shift towards more patient-centred care, even for children, while ensuring that each child is fully cared for by the family and receives adequate nutrition. In some instances, the child's parent/s may be hospitalized with TB.

Suggestion for TB screening. Children who contract TB from an infectious adult often do not present with a cough. Thus, it was suggested that the new issue of the handbook should include a history of contact with an adult case of TB as a bridge to the so-called cough entry point for screening. A history of contact with a known case of MDR-TB is especially relevant.

Overview of UNICEF projects in the WHO European Region with links to TB prevention and care

Dr Ruslan Malyuta, HIV/AIDS and Adolescent Health Specialist, Regional Office Europe and Central Asia, UNICEF

The mission of UNICEF is to ensure that the rights of every child are protected, including the right to health, development, nutrition, education and social protection. According to UNICEF, there were a total of 956 000 cases of TB among children (aged 0–14 years) worldwide in 2015. Although African countries have the greatest burden of childhood TB, 26 000 cases were in the countries of central and eastern Europe and the Commonwealth of Independent States (CEE/CIS). Although this figure may look reassuring because it is similar to figures for wealthier economies such as the United States of America, the situation is actually very worrying because it includes some of the highest numbers of childhood MDR-TB cases. Children still die of TB at a rate of almost 600 every day, and many of these are under 5 years old. It is estimated that only 7% of the 1.2 million asymptomatic children exposed to TB have access to preventive therapy. According to Dr Ruslan Malyuta, this is due to a

failure of health systems and represents an infringement of children's rights because nowadays TB is both preventable and treatable. She stressed that an equitable distribution of resources would give the best results and have the highest impact on the most marginalized groups in society.

Dr Malyuta presented a few case studies to highlight some aspects of TB infection that make it such a difficult and complex event in a child's life. Very young children (under 5 years old) are particularly prone to TB infection, especially if they are malnourished or infected with HIV. Uninfected children also suffer psychologically when they see close family members dying or suffering from TB. In addition, some infected children need painful injections every day, are hospitalized for many weeks and months, and are separated from their families without receiving adequate stimulation (e.g. housed in dreary wards with no toys or adult companionship). TB in children slows down their education and development, thus contravening their rights to a full education and to live in a supportive environment. UNICEF has a whole "cluster" dedicated to the social protection of children, which include not only nutritional support (e.g. through cash transfers) but also empowering communities to promote and support the well-being of children. Stigma and marginalization are common problems, which are shared with sufferers of other diseases, especially HIV, leprosy, and mental health problems. UNICEF interacts with many partners on the ground in in affected countries; thanks to strong advocacy, child-friendly FDCs are now available in some of these countries. Multisectoral partnerships are crucial to achieving the goals of the goals of the End TB Strategy. At the end of her presentation, Dr Malyuta discussed the upcoming meeting between the Government of Kazakhstan, UNICEF and WHO in preparation for the 40th anniversary of the Alma Ata declaration in October 2018.

Discussion points and comments

UNICEF as a source of BCG vaccine. UNICEF distributes many vaccines and has one of the largest humanitarian warehouses in the world, situated in Copenhagen. To date, the biggest donor to vaccine funding has been the Global Alliance for Vaccines and Immunisation. Only those countries eligible for grants from the Global Fund can receive free vaccines from UNICEF. However, ineligible countries can try to negotiate a price with UNICEF, and this may prove to be more favourable than local suppliers. UNICEF assumes responsibility for the condition of delivered vaccines up to customs clearance.

Vulnerable populations. Outreach workers have an important contribution to make in reaching vulnerable populations. Bulgaria has acknowledged this and has opened a public tender for nongovernmental organizations and civil society organizations to bid to provide some services specifically to vulnerable populations in accordance with a clearly defined set of terms.

Childhood TB in the EU and EEA

Dr Senia Rosales Klintz, TB Expert, ECDC

Countries in the EU and EEA reported that 2415 children aged under 15 years had TB in 2015, representing 4.2% of the total number of cases reported that year (n = 57 136). The burden of MDR-TB among children in the EU is unknown.

A descriptive logistic regression analysis of the TB surveillance data reported by all 26 EU Member States from 2007–2015 was performed to quantify the burden of MDR-TB, identify risk factors and assess diagnostic and treatment gaps among children in the EU. Croatia, France, Italy, Liechtenstein and Spain were excluded because data from these countries were not case based or did not cover the

entire study period. Geographical origin was determined by citizenship or country of birth and treatment outcome data was collected for 12 months for DS-TB cases and for 24 months for DR-TB cases (Greece did not report treatment outcomes). The analysis showed that out of 18 826 TB cases in children, 78% were not confirmed bacteriologically (in comparison, laboratory confirmation of adult cases was 80%), 22% were confirmed (4129 cases) and 18% did not have DST results (751 cases). Of the 3378 cases with DST results, 88% were DS-TB (2967 cases), 7% were mono-resistant (249 cases), 2% were poly-resistant (64 cases), 3% were MDR-TB (90 cases) and 0.2% were XDR-TB (eight cases). The countries with the highest numbers of MDR-TB cases were the United Kingdom, Germany, Romania and Sweden. Other countries with experience of MDR-TB in children were Lithuania, Latvia, Belgium, Norway, Netherlands, Austria, Bulgaria, Finland, Poland, Estonia, Ireland, Luxembourg and Portugal. In all, 83.9% of non-MDR-TB cases and in 78.4% of MDR-TB cases had a successful treatment outcome, but the 5–9 year age group was noted to be significantly associated with an unsuccessful outcome. No treatment gaps were observed. Conclusions from this analysis were that (i) laboratory confirmation of TB in children is difficult because of low mycobacterial counts and the anatomical site of disease (e.g. hilar lymphadenopathy is commonly found in children); and (ii) the real burden of MDR-TB in the EU is currently underestimated. This study also concludes that paediatricians caring for foreign-born children must have a high index of suspicion for TB, especially for MDR-TB. It also calls for better diagnostic tools to enable clinicians to diagnose TB more confidently in children.

Discussion points and comments

Refugees in the EU. It is unclear whether the recent refugee crisis in the EU has had any impact on TB epidemiology. The country of origin seems to be important. For example, some countries are finding that refuges from African countries are at a higher risk than those from the Middle East. Disease patterns among adults will probably be closer to the epidemiological trends in the country of origin. Countries that have accepted large number of migrants from the Middle East have so far not reported a marked increase in MDR-TB incidence. However, the difficult living conditions in some of the large camps and refugee communities are highly likely to lead to more cases of TB in the near future. There are some reports of problems for refugees in accessing primary health care (e.g. by UNICEF).

Definition of foreign born. The definition and classification of foreign born used in the study did not stratify by region of origin. The analysis stopped just before the mass refugee crisis that occurred towards the end of 2015. In some countries, children born to migrant families are considered citizens of the host country and thus may not be classified as foreign born. Such children may still have a higher risk of TB but this information might not be captured in the analysis if data collection is not refined to reflect this demographic.

Internal migration. The legislation enshrining freedom of movement for EU workers does not allow countries to screen individuals originating from countries within the EU with higher rates of TB. It provides a legal boundary to prevent discrimination among EU citizens. This is a complex matter and the idea of an EU health passport for internal migrants (as well as for refugees) is currently being discussed at higher levels across UN agencies.

Childhood TB: the Global Fund perspective

Dr Anna Scardigli, TB Disease Advisor, the Global Fund to Fight AIDS, TB and Malaria

Since its inception in 2002, the Global Fund has supported countries in their efforts to control HIV, malaria and TB, with HIV activities receiving the largest proportion of financial aid. Thanks to its sustained efforts, an estimated 22 million lives have been saved and the fund has paid for the treatment of 17.4 million TB patients, placed 11 million HIV-infected people on antiretroviral therapy and distributed 795 million mosquito nets.

Approximately US$ 100 million has been allocated for childhood TB. Funding opportunities include funding requests for TB modules, catalytic funding and special initiatives. Most countries have already submitted proposals for the US$ 11.1 billion available budget (2017–2019 allocation) and Dr Scardigli informed participants that there is some flexibility for countries to reprogramme unused funds. Countries are strongly encouraged to increase their co-allocations because the Global Fund is very keen to strengthen country ownership and sustainability. Catalytic investments are matching funds aimed at priority areas. Multicountry funds are used for selected cross-border critical initiatives. Strategic funds cover activities that are not covered by other allocations; they are often reserved for activities such as emergencies, strengthening community participation or conducting research. The fund has increased allocations for TB prevention and to meet the increasing demands of MDR-TB infection e.g. increasing access to rapid diagnostic tools such as GeneXpert and scaling up short-course therapy for MDR-TB. Other specific childhood TB activities include assisting the switch to new paediatric formulations and the use of digital X-rays. The fund will be investing US$ 190 million in 13 high-burden countries to identify bottlenecks in their health systems and identify missing cases of TB, including in children (Ukraine is the only eligible recipient in the WHO European Region). The outcome is expected to be the identification of an additional 1.5 million cases by 2019.

There is no specific module for childhood TB in Global Fund grant applications, and many countries do not differentiate between adult and childhood TB activities in their grant requests. Thus, it is difficult to trace the investment and actual expenditure on childhood TB. Dr Scardigli also outlined some special initiatives such as the initiative on programme quality and efficiency in Tanzania and Kenya, which will increase TB awareness by health care workers and thus improve the TB diagnosis. Case studies have also been collected to showcase best practices in maternal health and childhood TB.

Of more relevance to the Region is the financial support the Global Fund is giving to TB-REP in EECA countries to address the challenges of health system restructuring and financing as countries move towards more sustainable and efficient service delivery models. The document, A people-centred model of TB care: blueprint for EECA countries on modified models of care, was released in 2017 as a key deliverable of this project. Strong emphasis is being placed by the Global Fund on activities that include antenatal care, integrated community case management, combined integrated sexual and reproductive health/HIV services, and adolescent health. Dr Scardigli suggested that these could be used as entry points for funding for TB detection and prevention.

Dr Scardigli concluded her presentation by sharing some of the lessons learned. In her opinion, many countries are relying on a business-as-usual approach. Detection and access gaps remain and treatment success rates of MDR-TB have not changed much. Diagnostic algorithms are often too restrictive or do not take full advantage of new rapid diagnostic tools, and DST coverage needs to increase. Digital X-rays are good value but not widely used. Most grant applications do not prioritize active drug safety monitoring and management. Coverage of LTBI detection and treatment remains

low and many countries do not differentiate between LTBI and active disease in children. Furthermore, TB/HIV activity applications usually lack specific details. The role of the private sector and the services offered are not monitored, often do not make use of the new diagnostic technologies and probably do not report cases. The Global Fund encourages countries to be more ambitious in scaling up innovative approaches, tools and strategies to find missing cases and provides support for funding requests and grant implementation.

Discussion points and comments

Paediatric FDCs. Countries have relied on the Global Fund to supply first- and second-line drugs. As many countries now are transitioning from Global Fund support, all first-line drugs must be obtained through public procurement. This condition has been set by the Global Fund and use of the waiver mechanism will not be allowed from 2018 onwards. Some paediatricians and members of the medical community are worried that this will affect the quality of first-line drugs and the availability of paediatric FDCs. There are serious concerns that using suboptimal-quality drugs will enhance the risk of propagating drug resistance. This is a big problem and the Global Fund needs to revaluate its decision, especially regarding paediatric first-line drugs and FDCs. Ukraine is the only country in the Region that still receives catalytic funding.

Active case-finding. Many countries trace contacts but many do not report the outcomes and results of these activities. WHO recommends offering preventive therapy to children younger than 5 years but the recommendation for older children is conditional. As a result, many children miss out and do not receive preventive therapy. Contact-tracing practices and outcomes need to be given more importance, and the Global Fund can also take a more active role in supporting this move.

Clinical and public child and adolescent TB perspective

Dr Iveta Ozere, WHO Consultant

Dr Ozere related her experiences from Armenia, Belarus, Kazakhstan, Kyrgyzstan and Latvia in presenting to the group the main problems of childhood and adolescent TB and the measures needed to interrupt the vicious cycle that is preventing full implementation of the WHO End TB Strategy.

Early diagnosis should form the basis of TB treatment, especially among children and adolescents, but many cases are missed owing to failures within health systems. The proportion of children with TB varies, from under 5% in low-burden countries to 10–20% in higher-burden countries, and can reach 40% in very high-burden countries (i.e. over 1000 cases per 100 000 population). In the countries mentioned in this presentation, the TB rate ranged from 0.4% to 5% among children and adolescents. More specifically, in Latvia the data from 2016 shows that 3.9% (0–14 year age group) and 1.3% (15–17 year age group) of all TB cases were in children.

The low TB rate in children could indicate a strong TB programme; however, the speaker cautioned participants that they must remain vigilant because an incorrect finding of a small number of cases may be caused by failures in diagnosis and reporting while an incorrect finding of a high TB rate can indicate overdiagnosis. She also reminded participants that adolescents may have the adult infectious form of pulmonary TB and that the MDR-TB rate has increased in all of the countries mentioned, apart from Armenia.

National TB registries do not contain the necessary data to allow quality assessment of contact tracing and it is estimated that less than one child was evaluated for each source case. These registries should

be able to capture the number of children screened, any positive results, the number of children eligible for preventive treatment and the number receiving and completing preventive treatment. Molecular genotyping studies have demonstrated epidemiological links between children with TB and sources of TB infection. Dr Ozere strongly recommended that contact tracing should follow the stone-in-the-pond principle with three categories: (i) all close contacts; (ii) accidental contacts; and (iii) contacts in the community. She also gave the criteria for each category.

Close household contact: persons living in the same household as the source.

Close non-household contact: persons who have shared ambient air for a long period with the source (e.g. more than 8 hours continuously or over 40 hours in total), including unprotected health care workers exposed to acid-fast bacilli-positive cases during bronchoscopy and otolaryngology examination. For sources with MDR-TB-positive culture findings, a history of sharing a confined space (e.g. inside a car) is also included. Sources of accidental contact include frequent visitors, friends, classmates, schoolmates, relatives and colleagues at work.

Contacts in the community: persons who could have sporadic contact with the source in the community (e.g. at social events).

Dr Ozere said that in many countries it is often impossible to trace all contacts. Many high-burden countries have difficulties interpreting Mantoux tuberculin skin tests for the following reasons: boosted hypersensitivity, because a large proportion children undergo yearly tuberculin skin tests (many of these have no documented contacts but for some reason have been included in the high-risk category); over 95% of children have received the BCG vaccination; some countries still practice revaccination; and a test result with an induration of 5 mm or more is considered to indicate LTBI. IGRAs would have higher specificity in many of these children; however, WHO guidelines do not recommend that low- and middle-income countries replace the tuberculin skin test with this method of diagnosing LTBI (strong recommendation, low quality of evidence). Either the tuberculin skin test or IGRA can be used to detect LTBI in high- or upper-middle-income countries (strong recommendation, very low quality of evidence). There is some evidence in the scientific literature that sequential testing (i.e. the tuberculin skin test followed by the IGRA test for those with a positive reaction) is the most cost-effective method of detecting LTBI.

The speaker reiterated some issues highlighted by other presenters: the numbers of children and adolescents infected with drug-resistant strains of mycobacteria are unknown; and no treatment can be given or recommended due to an insufficient quality of evidence. The countries listed in the presentation follow WHO treatment guidelines and recommendations for the bacteriological evaluation of all children with presumed TB. These countries are all able to test biological specimens including gastric aspirates and induced sputum samples. Rapid molecular diagnostic methods (GeneXpert, Hain) and DSTs are also available.

Discussion points and comments

Hospitalization. Many parents of affected children are very concerned that routine hospitalization (often lasting for many weeks or months) results in missed school attendance so that children never catch up with peers. The move towards more child-friendly models of care may result in more cases being detected because families often hide their children from contact tracing teams from fear that their children will be taken away to sanatoria. On the other hand, some paediatric formulations may be more easily accessible in a more centralized hospital setting. Hospital referral should be based on a clinical indication such as adverse effects from the treatment.

Child contacts of MDR-TB cases. Isoniazid preventive therapy should not be given to these contacts, and there is no agreement or guidelines for further action. In some countries, child contacts are followed up radiologically, but the periodicity and duration of follow-up is variable. Contact tracing and record-keeping should be more systematic, and the team or individual performing the investigation should take responsibility for the thoroughness and outcome of screening efforts.

Terminology. The terminology used may be one cause of the insufficient attempts to identify children infected with TB. Use of the terms **latent**, **active** and **passive** may cause confusion or misinterpretation; for example, how should a child with radiological findings of calcified hilar lymph nodes but no other radiological evidence of abnormality be classified? Furthermore, use of the term **latent** does not indicate a need for any action to be taken by either the attending physician or the family.

Group work: reports from working groups

Working group facilitators were Dr Martin van den Boom, Ms Annemieke Brands and Dr Iveta Ozere

Dr van den Boom invited all participants to join one of the three working groups: a Russian-speaking group (for those who preferred to converse in Russian) and two other groups (divided by alphabetical order according to country name). The overall objective was to move current policies to improve TB care for children and adolescents. Topics of discussion were suggested, including limiting hospitalization, introducing FDC formulations, legislation, contributions from relevant partners, contact investigations, preventive therapy, and surveillance of childhood and adolescent TB. He asked the three groups to use the country posters as a reference to identify the top two or three most important challenges for countries, discuss how these can be addressed within the next two years and, finally, suggest what support is needed to resolve these issues. He suggested that discussions should be as free and open as possible, but that suggestions also should be practical, ambitious and realistic.

Group 1: Russian-speaking group

Dr Alexey Kazakov summarized the main challenges and possible solutions identified by members of the group, who mostly represented high-priority countries.

Priority 1: scale up ambulatory patient-centred care for children and adolescents with TB

Each country needs to define a set of criteria to determine where treatment should be given, whether in a hospital or outpatient setting. These criteria must place the interest of the child and the treatment outcome at the centre, and also take into account other factors such as the needs of the family and the availability of local services. Children receiving ambulatory care should be provided with adequate educational, financial and social support and should also receive proper nutrition. Continuity of care requires collaboration among paediatricians, infectious disease specialists (e.g. if the child is also HIV positive) and TB physicians providing primary health care. Civil society organizations also serve as effective liaisons between the patient, the family and the treatment centre. Participants also suggested that clear definitions are needed to guide the return to normal daily activities, especially the freedom to work (adolescents) and to return to school (children and adolescents).

Priority 2: financing of outpatient TB services

Many countries still do not have the correct structures for financing ambulatory care and there is often a lack of available public funds. This situation can be improved if money is allocated on a per-patient basis (rather than per hospital bed), with the money following the child to cover the cost of the ambulatory care package.

Priority 3: rational active case-finding and prevention

Active case-finding needs to be systematic and centred on contact tracing of children who might have been exposed to infectious adult TB patients. Standards and outcomes can be improved by using a standardized instrument such as a questionnaire to enable a more systematic approach. It could also direct the investigator to seek and report relevant risk factors and comorbidities. The stone-in-the-pond approach is recommended and a protocol describing the necessary testing procedures and duration of follow-up should be rigorously followed. The testing methods used to detect TB infection vary between countries, but it was suggested that the IGRA method should be available in all countries. Terms such as **latent**, **TB infection** and **preventive treatment** need to be revisited because they fail to convey the importance of preventive interventions in children and may lead doctors and parents or guardians to reject preventive therapy. The acceptance of contact tracing by families can be improved if they are offered some form of compensation. Similarly the team performing the active case-finding can be motivated by financial incentives.

Group 2: English-speaking group (countries A–Q)

Dr Florian Götzinger reported the group discussions on these countries, which included a mixture of low-, middle- and high-burden countries.

Priority 1: accurate reporting and consistent definitions

Earlier presentations in the workshop had indicated that all countries have missed and unreported cases of childhood TB. Following on from this, group members recommended that the issue of accurate reporting should be an important priority, especially for countries that claim they have no missing cases. The use of consistent definitions is essential to avoid confusion, for example LTBI (as yet, there is as specific International Classification of Diseases code), preventive treatment (often confused, even by TB specialists, so at-risk children are notified as cases) and treatment outcome (success versus completed).

Priority 2: determining the cost–effectiveness of mass screening programmes and preventive treatment

Not all countries have the same policies in this regard. Some high-burden countries still implement periodic mass screening programmes, but their cost–effectiveness is likely to be unknown or not monitored or reported.

Priority 3: identifying at-risk groups

At-risk groups may differ between and within countries and it is not clear what methods are used to define these and, therefore, who should be included. Questions such as who to screen, which methods should be used, which follow-up intervals and length of follow-up should be used, and which actions are necessary must be considered within the specific context of each country and the resources available. It is not possible to distinguish past exposure from recent reinfection and this can create a treatment dilemma, especially regarding very young children. Not all TB specialists may agree on how best to proceed, and some participants suggested that another round of preventive treatment may be warranted.

Priority 4: assuring quality and supply of BCG and tuberculin solutions

Some countries have experienced stock-outs of both BCG and tuberculin solutions that were caused by fluctuations in the supply and production of these reagents by pharmaceutical companies. The focal points for essential drugs and drug registration in the Ministry of Health might be able to help mitigate this problem.

Group 3. English-speaking group (countries R–Z)

Dr Peter Helbling reported the group discussions on these countries, which included a mixture of low-, middle- and high-burden countries.

Priority 1: management of MDR-TB in children

This priority is shared by all regional and global partners and action is required to advance our knowledge and understanding of managing childhood MDR-TB (disease and infected states) both safely and effectively. The expertise and level of understanding of all health care workers involved in the care of all children with TB, especially if drug resistance is present, must be continually updated because guidelines on TB diagnosis, management and treatment are constantly undergoing development. More research is needed to collect evidence on which to base recommendations and guidelines. All countries in the WHO European Region seek opportunities to encourage and facilitate this kind of research.

Priority 2: availability of paediatric first-line FDC formulations

Many country representatives are not experienced in using these formulations or may not know how to acquire them. Some depend on exceptional waivers because the drugs are not registered in the country (e.g. Bulgaria). It was suggested that countries within the European Medical Agency should start discussions with GDF to increase access to these formulations.

Priority 3: TB in adolescents

Adolescents often have the infectious adult forms of TB but in most countries are still under the care of paediatricians. This is challenging not only for the clinical care of these individuals but also for interpreting the routinely collected data. Management pathways and data collection practices for older adolescents should be revisited and clarified with a view to using cohorts with narrower age ranges (especially to distinguish the 15- to 18-year age group).

Priority 4: active case-finding and accurate reporting

TB in children is the result of missed diagnosis or suboptimal prevention. Contact tracing is the most effective active case-finding opportunity for this group, and countries should evaluate the results of their efforts. Immunosuppressed children (including those with HIV) should also be checked for a LTBI and treated accordingly. Some countries (e.g. Switzerland) systematically collect and report the results of contact tracing and use a cascade algorithm that records the size of the eligible cohort population, the results and the actions taken. Bacteriological confirmation of childhood TB varies across the Region and physicians should strive to confirm cases bacteriologically, avoid misdiagnosis or overdiagnosis (especially for tuberculous meningitis), and report the results.

Priority 5: screening of children in migrant/ refugee families

Countries in the Region may have unique circumstances that can lead them to identify specific high-risk groups (e.g. children in Roma families in Bulgaria, Syrian refugees in Turkey). Evidence of active case-finding in these groups is still unclear, but the overriding principle should be to ensure access to medical care when required. LTBI screening in these populations depends on the resources

available within the country and should respect ethical and legal boundaries. The group suggested not to "expand but [instead to] focus on the tip of the iceberg".

Other comments

- The need for clear definitions, criteria and concepts was accepted by all.
- There were some differences in current practices of testing for TB infection and prescribing preventive therapy to children who have recently been exposed to TB patients in low- and high-burden countries. For example, children in the Russian Federation undergo the Mantoux tuberculin skin testing every year and preventive therapy is recommend if tuberculin conversion has occurred. The IGRA is used for immunosuppressed (e.g. HIV positive) children who have been exposed to TB. If the test is positive, preventive therapy is prescribed immediately. The situation is different in Germany, where all close contacts younger than 5 years are immediately put on preventive therapy even if tuberculin negative. The tuberculin skin test is repeated after three months and treatment is stopped if there is no conversion. The rationale behind this protocol is the high rate of false negative results (up to 10%) for the IGRA and tuberculin skin test.
- Shortages do occur, and some countries have experienced shortages of BCG and isoniazid. The GDF can assist countries to avoid this as much as possible. As an example, in Kazakhstan the lack of BCG was associated with a large increase in TB incidence in unvaccinated children.

Suggested next steps

Required actions were identified by all three working groups. These could be jointly undertaken by country representative volunteers, WHO and technical partners.

1. Consider updating guidance on managing childhood TB specific to the WHO European Region that could be adapted according to the needs of Member States of this Region. The latest issue was released in 2014. The update should cover the following topics: TB symptoms; a review of diagnostic methods (update on rapid diagnostic techniques, including updated methods for detecting LTBI); recommended regimes for children with DS-TB and DR-TB; the use of paediatric FDCs and second-line drugs, especially for very small infants (less than 4 kg body weight); treatment for LTBI; clear definitions of infectious states; and special consideration of TB in older adolescents.
2. Develop detailed guidelines on detecting and managing contacts with DS-TB and DR-TB. These should include protocols for specific age groups.
3. Provide technical assistance to countries on managing MDR-TB in children and adolescents.
4. Collect, publish and disseminate examples of good practices from across the Region related to contact tracing, examination and management for both DS-TB and MDR-TB.

Dr Martin van den Boom thanked all the participants for their energetic discussions and for their practical suggestions for WHO actions. He informed them that some upcoming planned publications and reviews by WHO already address some of these priorities and will meet some of their demands.

- Updated guidelines on LTBI management in adults and in children are expected to be available in 2018.

- A new position paper on BCG vaccination will be released in 2018. This will include a section on HIV-positive mothers and children.
- The global Roadmap for childhood TB is being updated and best practices will be added. Contributions from countries are eagerly awaited.
- WHO is actively engaged with the Global Fund to ensure a constant supply of new paediatric formulations for first-line FDCs, child-friendly second-line drugs and short-course preventive therapy.

Conclusion

Dr Masoud Dara concluded the two-day workshop by showing his appreciation for the stimulating discussions and shared experiences. He asked participants to remain actively engaged in producing the scientific evidence that forms the basis of all WHO recommendations and guidelines. He acknowledged that open communication had been achieved throughout, despite the differences in language between countries. He reminded everyone of the growing burden of TB and HIV in the WHO European Region. Although there is a strong political commitment to address this, a more-integrated approach is needed to tackle TB in children. Words must now be translated into action and a new resolution is needed to ensure stronger integrated management by national TB programmes. He welcomed the suggestions from participants from all countries on the actions needed to address this challenge.

Dr Dara identified three areas of work that should be led by rigorous scientific investigations to strengthen progress in addressing childhood TB in the Region.

1. Investigations to improve the case detection rate and reduce the number of missed cases of childhood TB in the Region. This could start as a pilot active case-finding study in a high-burden country.
2. Investigations into managing children who are exposed to infectious adults suffering from M/XDR-TB. Studies are under way in South Africa but similar studies that take the regional context into account are needed.
3. Investigations into MDR-TB detection and reporting in children of different age groups. Rates of MDR-TB in children in the Region appear to be following different trends from those seen in adult confirmed cases, and the reasons for this need to be investigated. A collaborative fact-finding investigation in two or three countries would produce useful insights.

Dr Dara reminded participants of the upcoming high-level events due to take place in 2018. The 22nd International AIDS Conference due to take place between 23 and 27 July in Amsterdam, the Netherlands will include sessions on TB. The annual Union World Conference on Lung Health due to be held in The Hague on 24–27 October 2018 will focus on TB and other lung diseases. Also in 2018, the first ever UN General Assembly High-Level Meeting on TB will be a critical event that brings together heads of state to find solutions the TB epidemic an finally bring to an end the suffering from this disease.

Acknowledgements

This report was edited by Dr Masoud Dara, (Coordinator, Communicable Diseases Programme Manager, Joint Tuberculosis, HIV and Viral Hepatitis Programme, WHO Regional Office for Europe) and Dr Martin van den Boom (Technical Officer, Joint Tuberculosis, HIV and Viral Hepatitis Programme, WHO Regional Office for Europe). The rapporteur for the meeting was Dr A Galea.

Suggested reading

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Annex 1. Meeting agenda

WORLD HEALTH ORGANIZATION
REGIONAL OFFICE FOR EUROPE

WELTGESUNDHEITSORGANISATION
REGIONALBÜRO FÜR EUROPA

ORGANISATION MONDIALE DE LA SANTÉ
BUREAU RÉGIONAL DE L'EUROPE

ВСЕМИРНАЯ ОРГАНИЗАЦИЯ ЗДРАВООХРАНЕНИЯ
ЕВРОПЕЙСКОЕ РЕГИОНАЛЬНОЕ БЮРО

Regional Workshop on Child and Adolescent Tuberculosis in the WHO European Region	
Copenhagen, Denmark	**23 November 2017**
4–5 December 2017	

Day 1. Monday, 4 December 2017

Time	Topic	Speaker/lead
08:30–09:00	Registration	
09:00–09:30	Opening remarks	**Dr Nedret Emiroğlu** Director, Division of Health Emergencies & Communicable Diseases **Dr Masoud Dara** Coordinator, Communicable Diseases & Programme; Manager, TB, HIV and viral Hepatitis programme, Division of Health Emergencies & Communicable Diseases **Ms Oxanna Domenti** co-Chair, European TB Caucus
09:30–09:40	Presentation of objectives and appointment of chairs for the event	**Dr Martin van den Boom**, Technical Officer, TB, HIV and viral Hepatitis Programme
09:40–10:00	Overview of implementation of regional TB action plan 2016–2020, including childhood and adolescent TB-relevant content	**Dr Masoud Dara**
10:00–10:30	Discussion	All, Chair
10:30–11:00	Coffee break	
11:00–12:00	Poster session: part I	All, facilitators
12:00–13:00	Lunch	All, Chair
13:00–14:00	Poster session: part 2 Three countries present their posters to the plenary (one high MDR-TB burden country, one low TB incidence country and one additional country), including questions and answers, and discussion	
14:00–15:15	Discussion on major issues/challenges raised in the posters that need to be addressed in countries, in preparation for group work, support of TB Caucus on making the case for child and adolescent TB	Panel consisting of: Chair, representatives of countries which presented previously: one high MDR-TB burden country, one low TB incidence country and one additional country,

		Dr Martin van den Boom **Ms Rosanna Flurry** Regional Director for Europe and Central Asia, Global TB Caucus
15:15–15:30	Introduction of childhood TB friendly dosages and drugs in the WHO European Region	**Dr Maya Kavtaradze**, Regional Technical Advisor for Europe, StopTB Partnership's Global Drug Facility
15:30–16:00	Coffee break	
16:00–16:30	Update on new developments in diagnosis and treatment of childhood TB and global childhood TB perspective	**Ms Annemieke Brands**, Technical Officer, Global TB Programme
16:30–17:00	Discussion	All, Chair
17:00–17:15	Wrap-up of Day 1	Chair **Dr Masoud Dara**, **Dr Martin van den Boom**

Day 2. Tuesday, 5 December 2017

Time	Topic	Speaker/lead
09:00–09:15	Brief overview of contributions from the European working/task force group on childhood TB and update on exchange with another WHO Region (AFRO example)	**Dr Martin van den Boom**
09:15–09:30	Integration of childhood TB at primary health care level	**Dr Martin Weber** Programme Manager, Child and Adolescent Health
09:30–09:45	Discussion	All, Chair
09:45–10:00	Overview of UNICEF projects in the WHO European Region with links to TB prevention and care	**Dr Ruslan Malyuta** HIV/AIDS and adolescent health specialist, Europe and Central Asia Regional Office, UNICEF
10:00–10:15	Childhood TB, ECDC perspective	**Dr Senia Rosales-Klintz, TB** Expert, ECDC
10:15–10:30	Discussion	All, Chair
10:30–10:45	Coffee break	
10:45–11:00	Childhood TB, Global Fund perspective	**Dr Anna Scardigli** Disease advisor for TB, The Global Fund to Fight Aids, Tuberculosis and Malaria
11:00–11:15	Clinical and public child and adolescent TB perspective	**Dr Iveta Ozere** WHO consultant
11:15–11:30	Discussion	All, Chair
11:30–11:40	Introduction to group work: scaling up childhood TB prevention and care	**Dr Martin van den Boom** **Ms Annemieke Brands**
11:40–12:30	Group work session 1. Current in-country policy and national strategic plans (focus on persisting challenges and the extent to which childhood TB is not yet sufficiently covered)	All, facilitators (three groups as per introduction to group work)
12:30–13:30	Lunch	
13:30–14:30	Group work session 2. Based on session 1: how to move from current policy (taking into account key	All, facilitators (groups continued)

	challenges from group work session 1) to better care for children (e.g. through country adaptation of global policy and regional plan, limiting hospitalization, introducing fixed-dose combination drugs, legislation and contributions of relevant partners, contact investigation and preventive therapy, child and adolescent TB surveillance)	
14:30–15:30	Reporting back from group work: all groups (20 mins per group)	All, Chair, including discussion
15:30–16:00	Coffee break	
16:00–16:30	Identifying priorities for action based on group work reporting	All, Chair **Ms Annemieke Brands, Dr Martin van den Boom**
16:30–16:45	Country individual feedback session: adding to the key priorities on how to move towards better paediatric TB care	Collection of 3 priority points per country, facilitators
16:45–17:00	Participant feedback on the regional consultation	All, chair
17:00–17:15	Wrap-up, next steps, closing remarks	**Dr Nedret Emiroğlu** **Dr Masoud Dara** **Dr Martin van den Boom**

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[3] This designation is without prejudice to positions on status, and is in line with UNSCR 1244 and the ICJ Opinion on the Kosovo declaration of independence