MEDECINS SANS FRONTIERES

PAEDIATRIC TB CARE REPORT 2018

BREAKING THE CYCLE:

PAEDIATRIC DR-TB DETECTION, CARE AND TREATMENT IN TAJIKISTAN

CONTENTS

Executive summary 1

1. Introduction 4

1.1 Background 4

1.2 The global, regional & country TB burden 4

1.3 MoH/MSF collaboration 4

1.4 Evolution and adoption of developments 6

2. Finding cases, breaking the transmission cycle 8

2.1 Systematic active case finding 8

2.2 Infection prevention and control 8

2.3 Preparing for latent TB 12

3. Deploying diagnostics: on the right treatment, faster 13

3.1 Improved collection of samples for diagnosis confirmation 14

3.2 Diagnostic tools 15

4. Patient-centred care: individually tailored and comprehensive 17

4.1 Drug regimens 17

4.2 Innovating ambulatory care: family directly observed therapy (DOT) 20

4.3 Taking a holistic approach 22

5. Improving outcomes 25

5.1 Cohort description and main outcomes 25

5.2 Results and outcomes 26

6. Conclusion and recommendations 28

Bibliography 30

Executive summary

Tajikistan has one of the highest burdens of multi-drug resistant (MDR) tuberculosis (TB) in the world, according to the World Health Organization (WHO). Despite its ranking, alongside a number of countries in the region, there were only 743 reported incident cases of MDR-TB with 46 cases in children under 15-years-old in 2016. This is not unusual as global data is scant, incidence and prevalence typically underestimated and country reports lack accuracy, meaning the global burden of paediatric TB is poorly defined. Yet children aged under 15 years are particularly vulnerable to tuberculosis (TB) and those under five years are a key at-risk group.

Paediatric TB is not ignored in Tajikistan: in practice there has been a commitment to tackle the disease for a number of years. The Ministry of Health and Social Protection of the Population (MoH) and partners have been developing strategies and taking action to advance detection and treatment for this high-risk but neglected group. Incremental improvements in policy and practice are steadily charting a path towards an effective strategy for paediatric TB prevention and control in the country.

A successful partnership

Finding, diagnosing and treating paediatric TB remains a clinical and operational challenge, and a particularly urgent one in the case of MDR-TB. Médecins Sans Frontières/Doctors Without Borders (MSF) has successfully collaborated with the MoH in detecting and treating paediatric TB, with the number of patients admitted to the project increasing since 2013.

The programme employs international best practices and innovations to provide the best possible chance of a cure to patients. A key strength of this partnership has been the collaboration between the Republican Centre for Protection of Population from Tuberculosis national TB programme's (NTP) Consilium, the over-arching clinical decision-making body and MSF clinicians. In collaboration with MSF, NTP and Consilium have reviewed, monitored, approved and passed a raft of measures including active case finding, sputum induction, child-friendly formulations, new drugs and shorter regimens, enhanced infection control and holistic, patient-centred models of care.

These advancements have generated significant momentum and are beginning to show true beneficial outcomes for patients. Across the Central Asia region, Tajikistan is in the vanguard of some developments but still has more work to do on others. Nevertheless, each progression enables the MoH and MSF to gain more experience of what works. As the programme gathers practice-based evidence, it contributes to the body of knowledge on paediatric MDR-TB across the region and globally.

Objective and intended audience

The primary objective of this report is to continue to share the partnership's empirical experience with others in the region, and to drive the agenda forward in this often neglected but vital area of TB prevention and control. Through this report, and with the support of MSF, the Tajikistan MoH seeks to take a leadership role, positively influencing others committed to attaining the goals of the End TB Strategy (1). The report therefore is intended for:

- National MoH NTP and other national stakeholders – to document and showcase progress of paediatric TB detection, diagnosis and care in Tajikistan. Focusing on MoH/MSF areas of operation, there is reflection on sustainability, the challenges of the approaches, and discussion of the future if momentum on addressing paediatric TB is to be maintained.
- National TB programmes in the Eastern Europe and Central Asia region and beyond – to highlight best practice and innovations from case finding to drug regimens, and to demonstrate feasibility of findings, treating and caring for paediatric TB patients. Hopefully a demonstration of what's possible in Tajikistan may encourage adaptation and adoption by those countries in the region where such steps have yet to be taken.
- International stakeholders – to advocate for continued interest and innovation, support and commitment by technical and funding partners. Innovation, widespread implementation and scaling up detection, diagnostics and treatment for childhood TB are championed by the international community as essential to achieving the End TB and Sustainable Development Goals. Countries cannot do this alone and continue to require strong partnerships and support to help meet their commitments.

LIST OF ABBREVIATIONS

ACD1	ambulatory care from day one
CXR	chest x-ray
DR-TB	drug resistant tuberculosis
DS-TB	drug sensitive tuberculosis
DST	drug susceptibility testing
DOT	directly observed therapy
EECA	Eastern Europe and Central Asia
EU/EEA	European Union/European Economic Area
F-DOT	family directly observed therapy
HCAI	health care acquired infection
HIV	Human Immunodeficiency Virus
I/NGO	International/ Non-Governmental Organisation
IPC	infection prevention and control
LTBI	latent tuberculosis infection
Machiton	National Centre for TB, lung diseases and thoracic surgery
MDR-TB	multi-drug-resistant tuberculosis
MoH	Ministry of Health and Social Protection of Population of the Republic of Tajikistan
MSF	Médecins Sans Frontières
NTP	Republican Centre for Protection of Population from Tuberculosis, National TB Programme
PCC	patient-centred care
RR-TB	resistant to rifampicin tuberculosis
SCR	short course regimen
SDG	Sustainable Development Goals
TB	tuberculosis
UN	United Nations
WHO	World Health Organization
XDR-TB	extensively-drug-resistant TB

LIST OF FIGURES AND TABLES

Figure 1 *Chronology of major milestones, MoH/MSF paediatric TB programme, Tajikistan.*

Figure 2 *Flow diagram of the MoH/MSF paediatric TB programme contact tracing process, Tajikistan.*

Figure 3 *Age group distribution by sex, MoH/MSF Tajikistan Paediatric TB programme, as of June 2018.*

Figure 4 *Proportion of paediatric (<18 years) cases categorised by WHO child growth standards, MoH/MSF Tajikistan Paediatric TB programme patients*

Figure 5 *Number of cases (by treatment start year) and outcomes (by treatment end year), MoH/MSF Tajikistan Paediatric TB programme, 2011-2018.*

Figure 6 *Proportion of each regimen type, by year of starting treatment, MoH/MSF Tajikistan Paediatric TB Programme, 2011 to June 2018.*

ANNEX A

Figure A *Diagnostic algorithm for confirmation of TB in Tajikistan, Republican Centre for Protection of Population from Tuberculosis, March 2018.*

Table A *Key features of anti-TB drugs in use in MoH/MSF Tajikistan Paediatric TB programme patients, 2018* .

ACKNOWLEDGEMENT

This report is produced with the grateful acknowledgement of Tajikistan Ministry of Health and Social Protection of Population of the Republic of Tajikistan, the Tajikistan Republican Centre for Protection of Population from Tuberculosis and all MSF colleagues in the field. Importantly, we acknowledge our brave patients and their families; without their generosity in sharing their stories, this report would tell only half the story of childhood TB in Tajikistan.

1. Introduction

1.1 Background

The World Health Organization (WHO) deems tuberculosis (TB) a global health crisis, one responsible for the most deaths worldwide of any single infectious agent, surpassing HIV/AIDS. Though successfully controlled in many parts of the world, TB remains endemic in some countries with MDR-TB a major public health issue and a threat to the global prevention effort (2).

TB is an adaptable bacteria capable of genetic mutation that can result in drug resistance. Drug-resistant TB (DR-TB) is defined by failure to respond to at least the first-line antimicrobial drugs, isoniazid and rifampicin. MDR-TB can result from infection with the already drug-resistant (DR) disease or may develop during treatment. By 2006, XDR-TB (defined as MDR-TB plus resistance to one drug in each of the fluoroquinolones second-line injectable agents) was reported in all regions of the world and was classified by WHO as a serious emerging threat to global public health. By the end of 2016, XDR-TB had been reported by 123 WHO Member States (2) (3) including Tajikistan.

Children aged under 15 years are particularly vulnerable to TB and those under five years are a key at-risk group. WHO's Global TB Programme estimates one million children contracted TB in 2016, while 253,000 died from the disease in the same year, and approximately 10-11 percent of all TB cases are children (4). Nevertheless, it is likely that available figures under-estimate the true picture. The numbers reported by many national TB programmes fall well short of the expected range. Furthermore, data on childhood MDR-TB is scant to non-existent, but given the half million burden of the MDR strain among adults, annual estimates for children would be considerable (5). Moreover, there is a substantial gap between the number of children developing MDR-TB and the three to four percent that are diagnosed and treated. This gap means that likely 21 percent of children with MDR-TB will die (6).

Against this alarming backdrop, UN Member States endorsed the WHO End TB Strategy in 2014 (1), thereby committed to ending the TB epidemic by 2030. In partnership with MSF, the Tajikistan MoH is taking action on the Strategy's call for TB programmes to embrace innovations, expand services and provide a model of care that is comprehensive and patient-centred.

1.2 The global, regional & country TB burden

In accordance with 2015 global burden estimates, the WHO updated the highest burden country list for TB, MDR-TB and TB/HIV. Each list accounts for 85 to 89 percent of the disease(s) respectively. Tajikistan features alongside a number of Eastern Europe and Central Asia (EECA) region countries in the top 10 countries for MDR-TB burden. Together these accounted for 5.7 percent of global incidence in 2016 (2, 7).

In Tajikistan, recent MDR/RR-TB estimates of 19.9 percent of new cases and 41 percent of previously treated cases (8) significantly eclipsed the respective 2016 global estimates of 4.1 percent and 19 percent (2). In its 2017 WHO Country Profile Report (data from 2016) Tajikistan reported an estimated TB incidence, including HIV positive and TB co-infected patients, of 85 per 100 000 population, with an MDR/RR-TB rate of 30 per 100 000 population. Tajikistan estimated just 830 incident cases in 2016 among those aged under 15 years (9).

1.3 MoH/MSF collaboration

The MoH and MSF collaboration on paediatric TB care started in Tajikistan in 2011, when the first paediatric TB patients began treatment. There are numerous stakeholders working on TB in Tajikistan. Despite the various initiatives underway and support provided by other actors, MoH and MSF identified a gap in care for children and decided to focus on paediatric TB. Several key developments throughout the 2000s put Tajikistan on the road to tackling TB, including

starting MDR-TB treatment with support from partners in 2009. The inception of a comprehensive paediatric TB programme in 2011 cemented the MoH/MSF partnership with DS and later DR infected children entering treatment. The area of operations encompasses Dushanbe, Rudaki, Hissor & Vahdat.

The NTP/MSF partnership grew stronger as bolder measures towards meeting the End TB targets for the neglected area of paediatric TB became viable options. Since 2013 in particular, the Republican Centre for Protection of Population from Tuberculosis' National TB Programme (NTP) and MSF have together introduced many new developments in detection, treatment and curing paediatric TB patients.

Davlatmo Safaralieva has worked at Machiton TB Hospital since 2009 and is the senior nurse in the paediatric ward. Working in collaboration with MSF has proved a positive experience for patients and staff alike.

"I see the importance of joint efforts with MSF; it has resulted in improvements of all aspects of TB care, especially when it comes to paediatric TB. Before, we knew treatment only as giving drugs and it was sad to see the children in a low mood. Can you imagine this drug-intake with water and tablets only? It is not going to work for children, especially when you consider of the length of time it takes to be treated, and so the children would just not take the drugs.

Within the last few years, our approach in delivering care to children has gradually changed. Now, look at the things we are doing: family support, nutrition, a colourful playground for the children. These all help to create an environment for a child to stay motivated and continue treatment. It is so great that we do child-friendly dosages and have yoghurts, jams and peanuts which make drug-intake time so easy for both children and nurses. Children love it when the nurses put a star or smile on the chart for each proper drug-intake; it is like a score at school. Mothers are happy that their children are at the centre of our care."

Figure 1. Chronology of major milestones, MoH/MSF paediatric TB programme, Tajikistan

2011 – MoH/MSF collaboration on a Paediatric TB programme begins.
2013 – First paediatric TB diagnosis using sputum induction.
2015 – Introduction of GeneXpert and new drugs.
2016 – First patients treated with Bedaquiline & contact tracing ramped up to core programme activity.
2017 – Introduction of paediatric short course regimen & publication of revised National Paediatric TB Guidelines.
2017 – First patient on Delamanid and Bedaquiline combination therapy cured.
2018 – First patient managed by F-DOT achieves a successful outcome.
2018 – Ultra-cartridge detection trial – stool & sputum sample & introduction of TB LAM testing for HIV positive patients.

1.4 Evolution and adoption of developments

PROGRAMME LEARNINGS AND THE CHALLENGES AHEAD

The MoH/MSF paediatric TB programme has shown empirical evidence of the effect of innovations and interventions. Inevitably, each major learning is counterbalanced by certain challenges:

- Contact tracing is the gateway to finding cases among people most at-risk, who may remain hidden due to a range of reasons from the personal to the clinical. Scaled-up efforts and adequate resources are needed to replace passive with active case finding as the default strategy.
- New technologies for sample collection and diagnostic methods have substantially reduced the time spent putting patients on the right treatment. However, very limited availability of sputum induction, centralised laboratories and uneven distribution nationwide of the most rapid and accurate methods, means access to the right treatment as fast as possible is not yet equitable in Tajikistan.
- New drugs that are effective and well tolerated, as well as production of child-friendly formulas, give patients the best chance to stay adherent throughout treatment, while short course regimens return lives to normal sooner. Nevertheless, painful injections are still included in many regimens and manufacturers remain hesitant to develop child-friendly TB medicines. However, WHO guidance released in late 2018 seeks to establish the use of injectable drugs as exceptional, rather than part of the standard treatment.
- Through projects such as this, access to effective medicines has yielded successful outcomes. Global Fund transition, domestic procurement and regulatory complexities will complicate sustainable access to effective anti-TB drugs in the longer term.

Dr. Firuz Sharipov has been the director of Machiton Republican TB Hospital for the past four years. Since 2009, the hospital has been the main institution in Tajikistan treating MDR and XDR-TB adult and paediatric patients.

"What I have really noticed is that when innovations and approaches are implemented one of the main benefits is the adapted knowledge of staff. Working closely with MSF, regular trainings and consultations help to advance our staff approaches in treating our patients. Through recent developments over the years, such as lab upgrading, using new drugs in treatment regimens and infection control practices, hospital staff have gained up-to-date knowledge and experience.

As a result, we have completely changed the concept of training in the hospital. We have opened a training centre and created a training team so nowadays, doctors and nurses throughout the Republic come to get theoretical knowledge and undertake fieldwork when appropriate."

One of the main evolutions in tackling TB is the increasing emphasis on patient-centred care (PCC). This has been embodied by the idea that care should be driven by and responsive to patients' needs, while reducing personal and economic hardship and stigma. This pillar of the End TB strategy comprises:

- Early diagnosis of tuberculosis including universal drug-susceptibility testing; and systematic screening of contacts and high-risk groups.
- Treatment of all people with tuberculosis including drug-resistant tuberculosis; and patient support.
- Collaborative tuberculosis/HIV activities, and management of co-morbidities.
- Preventive treatment for high-risk groups; and vaccination against tuberculosis (1).

Mukhamadjon and his Grandma: Nine-year-old Mukhamadjon was diagnosed with extra-pulmonary MDR-TB after the death of his aunt and mother. His Grandma reflects on the arduous journey of diagnosis and treatment.

"Initially, I didn't know much about TB, even though two of our family members died of the same disease. My son used to tell me that TB couldn't be spread from person to person. But I presumed it was somehow infectious, so I thought parents shouldn't be kissing kids, keeping too close to them. Of course, my daughter, Mukhamadjon's mother, didn't like it when I said that.

At the beginning it was difficult and I lived every minute of it. It was difficult to endure all these medical check-ups, nine months of injection; Mukhamadjon used to cry and refuse to take his drugs. I found myself thinking that it would be good if injections were prescribed only when they were really needed and for shorter periods, not eight to nine months. After witnessing my grandson's suffering from a long treatment period, I wish doctors would revise treatment regimens, take out Paser and injections and replace these with easy-to-take drugs."

PCC therefore requires a holistic approach to manage the patient throughout their treatment including psycho-social and nutritional support, developmental stimulation, health education and integrated care across relevant services. The MoH/MSF partnership and training in aspects such as infection control, adherence counselling and nutrition support, has helped ensure these complementary aspects are incorporated into core medical supervision. However, there is a long way to go before such practices become the norm in healthcare facilities throughout the country.

2. Finding cases, breaking the transmission cycle

2.1 Systematic active case finding

The MoH and MSF collaborate to conduct systematic, active case finding in the project areas, screening families of all paediatric (DR-TB) and adult (DS and DR-TB) index cases – a method known as contact tracing. This is one way the programme works towards the global strategy aim of addressing systematically the challenges of caring for children with TB and child contacts of adult patients (10).

There is up to 80 percent concordance between DST results in DR source cases and infected children (11). It is estimated that contact tracing, based on all index cases of adults with MDR-TB globally, would result in over 12 times more children diagnosed and treated than are currently (6). For potential paediatric TB patients reporting recent close contact (< 12 months) with a person diagnosed with TB, contact tracing is an essential component of both diagnosis and treatment (11).

Contact tracing is an effective method to find 'hidden' cases whether owing to a lack of symptoms, health seeking behaviours, health education or stigma, latent TB or other reasons that mean particularly paediatric TB cases may go undetected in the community. It also provides opportunities for improving health education, detection of other health problems (e.g. malnutrition), increased detection in very young patients where disease progression is faster and less specific, and importantly strengthening infection control measures within the home. Together these activities act as primary prevention measures; modifying the environment and breaking the transmission cycle, breaking the cycle of transmission within families and more broadly in the wider community.

The process engages multi-disciplinary MoH/MSF teams comprising a doctor, nurse and counsellor who make visits to families of TB patients where appropriate. These teams conduct contact tracing - assessing the risk to household members, recording anthropometric measures, signs and symptoms, and starting the diagnostics process for suspects. Household contacts are followed up every three to six months depending on the risk posed by index case's TB positivity status.

When a child with suspect symptoms is referred for chest x-ray (CXR), the family is assisted financially with the transportation and medical costs associated with the test. This contributes towards minimising direct and indirect expenses so that no families affected by TB face catastrophic costs (10). Moreover, the provision of financial assistance in this instance represents something more fundamental – a comprehensive approach to patient care that is responsive to the needs of each individual family and patient.

2.2 Infection prevention and control

Substandard attention paid to healthcare associated infections (HCAIs) creates an environment conducive to transmission and spread of TB among patients, healthcare workers and ultimately the community. Healthcare workers should be acutely aware of transmission risk and readily implement stringent IPC. Knowledge of the disease, its transmission and the perceived threat of infection varies among staff, leading to varying standards of IC practices in treatment settings. This has serious implications for creating favourable conditions for disease transmission (12).

In the MoH/MSF Tajikistan programme, the focus of the infection control component is to identify potential infection risks, determine how transmission occurs and implement effective

prevention methods. Training is a core element of the collaboration between the MoH and MSF infection prevention and control (IPC) teams. This upskills staff on infection prevention and control measures including standard precautions, lab safety, personal protective equipment, waste management and sharps disposal, hand hygiene and other relevant topics. This capacity building is complemented by a number of approaches to reduce transmission of HCAIs, such as safe medical equipment reprocessing, including installation of ultraviolet germicidal irradiation lights and safe medical waste management.

The IPC team also works with the contact tracing team counsellors to advise on infection control in the home. Health education sessions provide information about the disease, plus prevention strategies and modes of transmission. Integrated IPC messaging and health education are integral to breaking the transmission cycle. With increased awareness, patients and their families can modify their environment to minimise the risks of inter-family transmission (13).

Working in collaboration with the IPC responsible person, the IPC team works in all 26 MSF-supported facilities. Each trimester, regular visits are scheduled for an IPC assessment to

The Azimov family (part 1): Two mothers, Gulnora and Gulrukhsor, whose families live in a shared compound, discuss how contact tracing revealed three of their children had been infected with XDR-TB. Gulnora talks about how the journey to a cure started.

"Grandma died in June 2016 and a week after the funeral MSF and government healthcare workers visited us at home. They started explaining about TB, telling us how it is an infectious disease and that we needed to be tested for it ourselves. At the beginning we didn't realise we could get TB by being a contact of the infected person. Of course, when grandma was sick and taking treatment, health workers told us that TB was an infectious disease, but we didn't understand how we can get it.

We went to a health facility and had X-rays and there was other screening for the kids. We didn't even suspect that our children may have TB and we were shocked when we were told. The doctors told us there is treatment, drugs and support but it was still difficult for us to accept this. The whole family gathered together to discuss it and in the end, we decided that our children should get treated and hopefully cured."

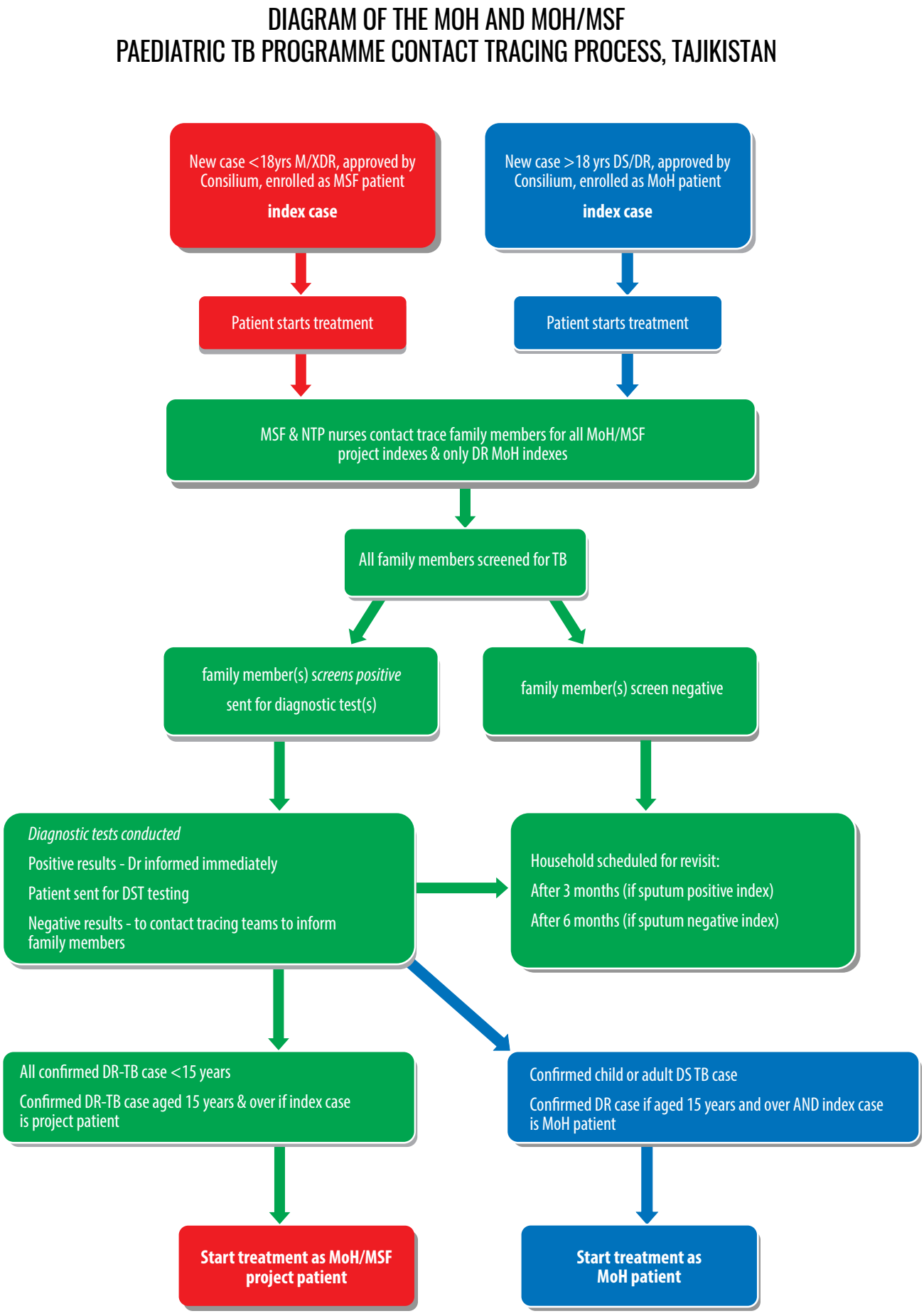


Figure 2. Diagram of the MoH and MoH/MSF paediatric TB programme contact tracing process, Tajikistan

identify gaps based on the 'Minimum IPC, Water and Sanitation Requirements' of the programme. This informs the development of an IPC strategy – a necessary foundation for monitoring performance and maintaining standards against the risk of healthcare associated infections.

2.3 Preparing for latent TB

The WHO defines latent TB infection (LTBI) as "a state of persistent immune response to stimulation by Mycobacterium tuberculosis antigens with no evidence of clinically manifest active TB." Only some 5-10 percent will go on to develop the disease, although age is a factor with younger children more inclined to progress to active disease. The global burden is not proven, however treatment of LTBI to prevent development of active TB disease is a major element in the End TB Strategy.

> *"Compared to previous practice, we have seen a lot has changed regarding infection control measures. For example, instalment and maintenance of UV-lamps both in patient rooms and corridors, plus good stocks of appropriate respirators and masks. This is very important to prevent TB transmission. Now, I am glad we have a specialist designated to infection control activities. He does regular assessments of all devices making sure infection control is in place to provide safety for both patients and staff."*
>
> **Davlatmo Safaralieva**, senior nurse, Machiton TB Hospital Paediatric Ward

The WHO recommends specific efforts to diagnose and treat LTBI in particularly at-risk groups, including children aged under five years who are household contacts of bacteriologically confirmed pulmonary TB cases. In 2018, the criteria for inclusion in LTBI treatment was expanded to include children testing positive for LTBI (14). Among the End TB Strategy Top 10 indicators set for global and national levels to achieve, the recommended target is that by 2025 there should be ≥90 percent LTBI treatment coverage for household contact children aged under five years (2).

Confronting this challenge, in 2019 the MoH/MSF project plans to treat latent DS-TB with new drugs, new approaches and using new tests to identify the infection. The current test used to identify LTBI is considered either obsolete and/or subject to interpretation. Conversely, QuantiFERON is a test

with easily interpreted results which rely less on subjective interpretation. Tackling latent DR-TB is an important step for the future. Currently, WHO recommendations regarding latent DR-TB remain unclear.

A strong contact tracing system is a pre-requisite for diagnosing and treating LTBI, making Tajikistan better placed than many other countries to take this next, vital step towards the End TB targets. Bacteria can remain dormant in the host, avoiding detection and treatment, and posing a threat to the host and others. Treating LTBI before it progresses to an active TB infection is an area attracting international attention.

TACKLING CHALLENGES

- Stigma and fear preventing timely health seeking:

Anecdotal evidence from MoH/MSF patients states that lack of awareness, fear of stigma and economic constraints delay some people from taking early action when signs and symptoms of TB occur in children. Health education including infection control must be a standard part of training for both healthcare workers and families of TB patients. At a societal level, governments and healthcare workers must continue to disseminate messages that dispel the myths and prejudices that contribute to the stigmatisation of TB suffer-

ers. This is particularly important for children for whom isolation can be devastating for their development and psychological well-being.

- Symptomatic and asymptomatic children going below the health worker's radar:

Either asymptomatic or undifferentiated symptoms common to childhood TB, plus the greater occurrence of extra-pulmonary TB among them, mean finding every case demands commitment at all levels – from national leaders to community-based health professionals. Healthcare workers at all levels need to be alert to the possibility of TB when children are presenting with a broad range of symptoms. They need to actively probe and investigate where there may be vulnerable children in a family; and they should be assessed using the latest methods for diagnosis and treatment. Regular training for healthcare workers is needed to keep knowledge on best practices up-to-date and forums that facilitate sharing of experiences, to ensure there is knowledge transfer from MoH experts and not only from external sources.

"Stigma and lack of knowledge is still present, and we also see that people, especially in rural areas, go to mosques to seek for advice. If we all, MoH and others in the TB community, include training Mullas and schools in the agenda, I am sure people will be less stigmatised knowing that TB is curable disease."

Dr. Firuz Sharipov, director of Machiton Republican TB hospital

3. Deploying diagnostics: on the right treatment, faster

Obtaining biological proof of TB in children is more difficult than in adults (15) and TB often goes undetected as children may suffer non-specific symptoms making diagnosis more difficult (5). Contact tracing is indispensable to the diagnostic process. Tracing adult index cases and taking a comprehensive history of close contacts can provide a major indication of the child's DST pattern in the absence of biological proof, which is highly likely to be the same as the contact. Alongside other tools that indicate the presence of the disease such as CXR, contact tracing aids determination of a more accurate and appropriate empirical regimen.

Micro biological and molecular screening and testing are vital for case finding, as well as case management, yet many countries experience lengthy and/or suboptimal diagnostic processes, failing to find cases early and determine specific drug resistance patterns (16). Rapid molecular tests provide results faster, cheaper and using less laboratory infrastructure, allowing countries to shift from periodic surveys to routine surveillance of MDR-TB (17).

Tajikistan faces the same challenges as many countries in that requests to its National Reference Laboratory have been exceeding capacity. More advanced options were not widely available and resource constraints with consumables made it difficult to ensure universal access to the best diagnostic methods. Since 2018 however, there have been increases in available GeneXpert machines and their cartridges, which provides some easing of the bottleneck that can occur.

Alongside this innovative sample collection, methods that enhance the quality of materials needed for accurate diagnosis have been aiding the National Reference Laboratory to determine exactly the individual child's DST pattern whenever possible. This, alongside the clinical indicators and patient's medical history, then enables MoH/MSF paediatric TB patients to be started on the right treatment faster. This helps to reduce severity and transmission thereby making substantial progress towards comprehensive treatment and control (1).

3.1 Improved collection of samples for diagnosis confirmation

As TB is predominantly found in the lungs, the sputum is the most commonly used material for diagnosing the disease. In the case of extra-pulmonary TB for example, other materials such as lymph node aspirate, cerebral spinal fluid and others (depending on the site of the disease) can be used for confirmation. Children struggle to expectorate sputum and often have paucibacillary disease (18), meaning the quantity and quality of the sample is substandard for testing and determining results.

"Through my work handling the drug and material orders from all areas of the hospital, I grew interested in diagnostic developments and when speaking with colleagues I learned more about GeneXpert and HAIN. Since we started using these tests I see patients start treatment earlier than before and I also noticed that based on their tests, patients receive different treatment regimens. I am glad for this because each child gets appropriate treatment."

Islom Eshonkulov, chief nurse, PD hospital

3.1.1 Sputum Induction

Sputum induction utilises a nebuliser machine through which the child inhales concentrated saline solution, that leads to coughing and sputum production. Although not pleasant, it is a more child-friendly method for deriving sputum samples than some other existing techniques, with a sample yield comparable to three gastric lavage procedures. Plus, it is safe for children and even babies from the age of one month old. Sputum induction is routinely used for MoH/MSF patients but its application for paediatric TB suspects outside programme rayons is not widespread. This means the opportunity for TB status confirmation and DST continues to be limited for many suspect cases.

If sputum samples cannot be obtained, cases are started on empiric regimens based on the DST pattern of the adult contact. This method remains an invaluable part of paediatric TB diagnosis: the majority of children can be started on appropriate treatment if the DST pattern of the adult contact forms an integral part of the diagnosis and regimen design.

However, this still leaves many children who will not be started on the right treatment for their individual DST pattern. This may result in extended time of treatment, allowing the disease to remain infectious for longer and increased risk of failure and amplification of resistance pattern. The extra dimension offered by sputum induction is equally critical to the success of an active case finding strategy, because it contributes further assurance that individually accurate detection and treatment is achieved.

3.1.2 Gastric lavage

Gastric lavage is a tool many countries continue to use for sample collection in paediatric TB suspects, however the MoH/MSF programme has not pursued its use after poor acceptance by the community. The method involves passing a tube down through the nose and into the lung and is an invasive and uncomfortable procedure for a child to endure.

Families often refuse permission for this as they understandably do not wish to see their children put through an unpleasant process. As the sample comes from the stomach, special measures are needed to ensure stomach acids does not kill the TB bacteria before it is analysed, including overnight hospitalisation and conducting the procedure on an empty stomach. Added to this, delays in delivering samples in a timely way to the national lab can mean the sample is compromised before it arrives, leading to false negative diagnosis. Hence, where sputum induction is available, it is the preferred option for clinicians and parents alike.

3.1.3 Stool collection

In early 2019, MSF began piloting detection of TB in stool samples. This may prove a real advancement in TB detection as stool samples provide the least intrusive method for paediatric patients, among whom bacteriological proof is notoriously difficult to obtain. The pilot will measure and document practices and results to determine if the enhanced sensitivity and specificity of new GeneXpert cartridges may potentially make it possible to diagnose from stools infection with a DR-TB strain.

3.2 Diagnostic tools

The diagnostic algorithm in Tajikistan employs all methods in line with WHO recommendations to determine TB infection:

- *GeneXpert* is the preferred diagnostic tool, allowing the smear or culture microscopy step to be omitted. *GeneXpert* gives a result indicating resistance to the first line drug rifampicin - effectively confirming MDR-TB within two to four hours.
- *The Hain* test is a sophisticated genotyping method that can determine MDR and XDR status from positive sputum or cultures. Furthermore, it determines resistance to a number of drugs including the injectable component of the traditional treatment, theoretically producing test results in around six hours.
- *Sample culture* remains the gold standard test for TB positivity and this enables the DST pattern to be detected.
- *Chest X-ray (CXR)* alongside clinical assessment and patient history, may be the only indication that a child may be infected. It is an important option available to the MoH/MSF contact tracing teams as a first screening method for suspected cases.
- *Smear microscopy* is a widely used diagnostic tool. However, since the 2018 update of the diagnostic algorithm, it is only performed after the TB diagnosis is confirmed in order to determine how infectious a patient might be.

Shamigul and Mohina (part 1): Shamigul has been a dedicated caregiver to her seven-year-old daughter, Mohina, since she contracted both pulmonary and extra pulmonary MDR-TB following her father's death. Mohina went undetected for a long time before enduring an exhaustive diagnostic process.

"I knew the screening procedures were not pleasant, so I asked Mohina's grandpa to go with her. If I was there she would cry more, but with her grandpa she was ok. Grandpa told me that the doctors did an X-ray and sputum induction. They asked if she could produce sputum, but she couldn't. Then they explained about the sputum induction method and said it was not a painful procedure, even if it looks unpleasant. Grandpa and Mohina agreed because she was tired of the disease symptoms and we knew she needed to start treatment as soon as possible.

When it was confirmed that it was TB, curiously enough, we were glad there was a name for the disease that we couldn't figure out for the whole year [had been making Mohina sick]. We were wondering what disease she had and why she wasn't getting better. But then, I started worrying whether she could be cured."

Each diagnostic tool plays a critical role in improving the speed and accuracy of diagnosis, illustrated in the NTP diagnostic algorithm *(Annex A, Figure A)*.

In early 2019, the MoH/MSF project has also introduced the TB LAM test to detect TB in the HIV positive population. This is a urine test that acts as a screening tool to detect TB in severely ill HIV positive patients or those with a CD4 <100, both groups particularly difficult to diagnose due to the severe immunosuppression. The introduction of TB LAM will be a step towards integrating TB and HIV testing and overcome the gap in diagnosis of TB in this population.

> *"Before, we had to wait a long time for DST results, up to 72 days. Now we have Hain, which takes three days maximum and MGIT results in two weeks so the time has reduced. It is also good that we can distinctly clarify a patient's DR resistant pattern; the lab specialists are happy to have moved on from the old practice. However, I heard there are new lab reagents that can identify the type of TB – DS, MDR, XDR – within an hour. I wish we could have them in order not to wait for three days or a week. It could help us to start treatment immediately."*
>
> **Dr. Asliddin,** chief doctor, XDR ward, Machiton Hospital

TACKLING CHALLENGES

Availability and access:

Presently, sputum induction is only available in the MoH/MSF programme, presenting a major stumbling block to finding and treating DR-TB in children nationwide. Given the difficulties outlined above for children to produce valid sputum samples, CXR, patient history and adult contact DST pattern are important leads to clinical diagnosis and proposed regimen. Clearly though, there is no substitute for correctly determining the individual child's DST pattern. Widespread access to sputum induction would significantly improve detecting and correctly treating paediatric TB.

A centralised laboratory system puts a burden on transportation and likely results in reduced access in rural areas. Placing GeneXpert machines in high burden rayons, and the support these machines can provide to neighbouring rayons, helps to overcome this challenge. Nevertheless, proximity to the equipment varies widely; so, while the capacity to get children started on treatment the same day exists, in reality challenges of sample transportation and slow return of results mean treatment time may be extended from hours to days.

Resource capacity, over-demand:

The challenges with reagent stock and supply means that the regional labs and NRLOZ are frequently unable to conduct even first -line testing and must send samples to NRL. Unavailability of onsite DST testing contributes to a backlog of work for NRL, leading to extended delays that can see DR results take months to be returned to family doctors and their patients. These delays negatively impact patient health and increase transmission risk in the community.

> *"I want the lab to be decentralised, because currently it can take up to two or three weeks until we receive test results."*
>
> **Dr. Nigora**, TB doctor, Polyclinic 9, Dushanbe

4. Patient-centred care: individually tailored and comprehensive

4.1 Drug regimens

Individual regimens depend on a number of patient-specific factors such as history, DST pattern, current condition and HIV status, as well as physiological indicators such as age and weight. DR-TB regimens require use of four effective drugs in the intensive phase and three effective drugs in the continuation phase. A grid at Annex A (Table A) brings together the range of drugs available and compares these across some of the main clinical and pragmatic considerations for composing regimens.

The Guidance for the Diagnosis and Treatment of Tuberculosis in Children of the Republic of Tajikistan, 3rd revised edition (The Guidelines), was developed by MSF and adopted by MoH in 2017. This indicates the short course regimen (SCR) as standard treatment for paediatric TB cases meeting the criteria. The SCR reduces treatment from 24 to 9-12 months for suitable patients and in 2017, Tajikistan was one of only two countries in the EECA region to include WHO recommendations in their national guidelines (19). Since mid-2017, MoH/MSF patients no longer receive the conventional regimen; only SCR and individual regimens are used.

The Guidelines also include sections on Delamanid and Bedaquiline. These two new drug options for DR-TB patients are no longer under the 'compassionate use' umbrella in Tajikistan but are an accepted part of the arsenal of drugs for fighting TB. The WHO global TB strategy Framework called for operational research as the way to build practice-based evidence in the area of new drugs such as Bedaquiline – the first addition to TB medicine in some 50 years – while also recommending Bedaquiline for treatment of severe DR TB (10).

MoH/MSF programmes are contributing to this body of knowledge with empirical evidence, while executing absolute caution and commitment to patient safety by monitoring adverse events. This has been successfully manifested in new WHO guidance released late-2018 that reclassifies Bedaquiline as a priority TB drug, with Delamanid to be reassessed for reclassification in the near future (20).

A case-by-case approach is also indicated in *The Guidelines* for prolonged Bedaquiline and Delamanid use beyond 24 weeks under certain circumstances, as international cohorts have demonstrated favourable outcomes (21). This is echoed by the programme's own findings detailed later in the results section. Although the WHO does not recommend their combined use while waiting for the evidence base to build, Bedaquiline and Delamanid have been used in combination in a few of the programme's regimens. To date, Bedaquiline, Delamanid or a combination of the two has been approved in the regimen of 68 MoH/MSF programme cases.

This virtuous circle has also informed the inclusion of the new drugs into *The Guidelines*. These new drugs are pivotal in changing the way paediatric DR-TB is treated, gradually turning the disease prognosis from improbable to curable. Among programme patients the drugs are being well tolerated and successful outcomes are being achieved. Adverse events to individual drugs as noted by patients in the cohort are documented in Annex A Table A, although no major adverse events have been reported.

Three of the MoH/MSF programme paediatric TB patients have been permitted to start regimens completely free from injections. This is not least in recognition of the evidence that ototoxicity in children is considerable, at more than 20 percent, and is only expected in regimens containing injectables. Occurring as this does during key stages in a child's development, there is consensus that injection-free regimens will be invaluable in improving MDR-TB treatment with a five-year view towards complete elimination of injectable agents an important goal (15, 22, 23). Moreover, the new WHO guidance also reflects the move away from injection-based regimens, with kanamycin and capreomycin no longer recommended TB drugs and other injectables deprioritised (20).

Adopting the evolutions in drug regimens, and bringing the latest developments to more patients, offers reduced treatment duration and improved chance of a cure. New drugs, however, do not present a miracle cure – three adult Delamanid patients did not have successful outcomes having presented late and gravely ill; each survived less than one month into treatment. This highlights that getting patients on the right treatment quicker genuinely is a matter of life and death. With the MoH/MSF Paediatric TB programme contributing to the evidence that successful outcomes can be achieved with innovative regimens across a range of clinical circumstances, more patients will hopefully continue to benefit from the phasing out of older, less effective treatments, including injections.

Child-friendly formulations such as those being introduced in Tajikistan from late-2018, will provide relief for patients and make adherence

> *"We use Bedaquiline whenever there is a chance as we see it helps to impact patient's condition. We have been prescribing it for six months and so far, there have been no problems with drug side-effects. We see a great effect with this drug during treatment. Even in the case of side-effects, we have all the drugs we need to manage these, and patients do not have to buy additional drugs. I also find short course treatment is very effective for patients with less severe TB and/or at an earlier stage. Why treat that category of patients for two years, when they can get cured in 9 to 11 months?"*
>
> **Dr. Nigora Badridinova**, TB doctor, Polyclinic 9, Dushanbe

Dr. Asliddin Islomov has been chief doctor in the XDR-TB ward at Machiton National TB Hospital since 2009. With extensive experience working with the most difficult cases, Dr Asliddin reflects on the developments he has seen in treatment of the previously virtually incurable strain of the disease.

"I learned about Bedaquiline when in 2015, MSF treated five patients with this new drug in their regimen. We participated in this pilot to observe and knowledge transfer of how to administer this new drug – that's when we saw its effectiveness. At some point I was wondering - why only five patients? Later, we found out that access to this drug was limited and it was expensive, but I know now it is more widely available for patients. I am glad we are open for innovations and making new drugs accessible for patients. In practice, with Bedaquline we see improvements in patients' recovery. As soon as we prescribed this drug in the regimen, lab results were TB negative in one month. That is great.

I remember one patient from Rudaki district; relatives brought him into hospital in a severe condition and he was lying on stretcher. Going through the treatment history we saw there was a very low chance we could help him. After we discussed the case in Consilium, I advised to include Bedaquiline in his regimen. All doctors agreed because there were no other options and they knew Bedaquiline could be effective. In four months or so he could already walk and in six months he was discharged, we wished him good health and hoped he wouldn't return to hospital. My colleagues managing the ambulatory phase tell me he is doing well and adhering to treatment.

It is rewarding to see that discussions in medical Consilium consider the individual needs of a patient. While taking an individual approach doctors consider lab results, drug tolerance history, plus body responses to side-effects, if there are any. This is a new concept in case management, where decisions are made collectively taking into account the patient needs holistically."

– especially for the youngest patients – more viable. In the meantime, children are severely under-served in terms of suitable formulations and dosages. Bespoke compounded formulations in a syrup suspension are specifically prepared by the MSF pharmacist for certain programme patients who simply cannot manage to swallow tablets. These allow for exact dosages reducing imprecision and changes to bioavailability that can be introduced when pills are cut or crushed to adapt the milligram strength of an adult dose tablet. They also improve palatability with flavourings. Consideration of formulations, dose and palatability are all imperative in developing new paediatric drugs (15). However, syrups have a very short expiry period – two to four weeks – which presents distribution challenges and makes larger scale manufacture unlikely.

TACKLING CHALLENGES

Improving acceptance and access:

The increased acceptance of new drugs in TB regimens is welcome, and the new WHO 2018 guidance propels treatment further along that trajectory, although there is still some way to go. Sustainable access to effective drugs must account for the legal, regulatory and administrative factors of drug registration and procurement. Even once drugs are registered, and pathways clearly established, the process of procurement remains a complex and challenging issue. Together with partners, the MoH needs to establish mechanisms that expedite drug registration, but at the same time, global distribution channels need to work alongside those national procurement mechanisms.

> *"Drug compounding, basically having drugs in a child-friendly syrup, makes our work with children so much easier; children are happy. In the past, we had to work hard when each child started treatment, not every child would accept lots of tablets every day."*
>
> **Islom Eshonkulov**, chief nurse, PD hospital

Child-friendly formulas and ever-more effective regimens:

While steps are being taken to manufacture and use more child-friendly formulations, this is still only the case for a limited number of the most effective drugs. The MoH/MSF experience with drug compounding and use of syrups has helped steer advocacy efforts, influencing the global push to develop child-friendly second-line formulations. Advocacy efforts must be maintained to find viable and sustainable solutions to meet the needs of under-served paediatric TB patients globally.

4.2 Innovating ambulatory care: family directly observed therapy (F-DOT)

Patient-centred care brings together approaches that seek to minimise the challenges of enduring TB treatment in pursuit of greater adherence, better outcomes and reduced opportunities for transmission. In the case of paediatric TB care, the MoH/MSF innovations in drug compounding and family DOT align with the global strategy of "… developing and using child-friendly formulation of medicines and family-centred mechanisms for enabling adherence…" (10).

The importance of offering ambulatory care from day one (where appropriate) for the patient is well recognised in Tajikistan, and the internationally established directly observed therapy (DOTs) model is in common use. Since April 2017, MoH/MSF have been offering an even more patient-centred approach – family DOTs (F-DOT). This takes the traditional DOT model of care and replicates the key principles but gives greater autonomy, flexibility and agency to families to manage TB within the homes. This step is in accord with the global TB strategy which calls for "patient support to extend beyond health facilities to patients' homes, families, workplaces and communities" and the roadmap for childhood TB that emphasises integrated family- and community-centred strategies (5, 10).

A monthly review of paediatric patients allows a multi-disciplinary team to decide if the patient profile is suitable for this model of care. If so, daily care for the child will be administered by a dedicated F-DOT supporter, usually a caregiver in the home. There will be intensive counselling and training for both child and the F-DOT supporter, routine visits at the health centre, plus ongoing adherence assessments.

The Azimov family (part 2): Gulrukhsor's son Azam was treated in hospital for eight months, then received care for a further four months as an ambulatory patient.

"When we were offered F-DOT we accepted it without thinking, because the first thing that came to mind is we don't have to walk two kilometres to the DOT centre every day. We were taking turns bringing the kids there every day and we had to leave our other children at home, where someone else needed to look after them.

It is so good that you stay at home with the children and the fact is with F-DOT you participate in treatment; you can act yourself, you don't need to wait for someone coming and treating your child."

MSF developed standard operating procedures and a toolkit to guide decision-making and implementation of F-DOT. Presently, patient eligibility depends on various factors including:

- A good history of adherence
- Supportive, treatment-literate family
- Simple regimen[1]

Group counselling sessions for hospitalised patients are held twice a month at the paediatric hospital where caregivers can talk and learn more about how to support their children through their treatment. This includes techniques to keep children engaged and interactive, to help them cope with the difficult journey ahead.

The Psycho-Social Team (PST) has found patients and caregivers truly value these interactions as it can be lonely and isolating having TB and caring for a child with the disease. Patients may also lack people to talk to who can empathise. Added to this, many are fearful of being stigmatised and so do not reach out for support. Others experience real stigma, and this can substantially add to the burden they carry. But, with support and understanding, some people have been able to address stigma and turn it around for a positive outcome.

> *"I know F-DOT has officially started this year and I am happy about it. We started this [community-based] practice before as there was already a need for it. Sometimes, patients call and inform us that they won't be able to attend health clinics due to an increase in public transport fees or household activities. Since this happened repeatedly, our policlinic administration agreed we should train community nurses in administering drugs."*
>
> **Dr. Nigora Badridinova**, TB doctor Polyclinic 9, Dushanbe

4.3 Taking a holistic approach

4.3.1 Adherence counselling and health education

Patient-centred care requires a 360-degree approach to supporting patients through treatment and MoH/MSF buttress clinical care with best practices such as psychosocial and nutritional support. A dedicated MSF psychosocial team (PST) provide counselling and support to patients at DOT centres, polyclinics, hospitals, TB dispensaries and sometimes at patients' homes.

An initial assessment and treatment plan ensures that the psycho-social needs of all patients enrolled in the MoH/MSF programme and their family situation is evaluated at the start of treatment. Counselling sessions with hospitalised and ambulatory patients start intensively and continually adapts in line with the patient's responses and ongoing needs.

> *"For people like us, we need health education meetings in our community about TB and other diseases so that we will know the symptoms and address them in time. Also, regular community medical check-ups would be helpful."*
>
> **Shamigul, Mohina's mother**

For ambulatory patients, counselling can be individual or held together with caregivers. Bi-monthly, there are separate group counselling sessions for teenage patients and parents. The idea of these sessions is to encourage greater discussion and sharing of ideas, advice and support among peers. Peers are an inspirational source of knowledge and advice because no one understands living with TB like those who have the disease and those who are caring for them.

4.3.2 Uniquely child-focused support and activities

A major disadvantage hospitalised children face is missing school. To help combat this, the programme employs teachers to provide basic schooling, enabling a smoother transition back to education once they are under ambulatory care. In addition, the PST brings an innovative dimension to the hospital setting – play therapy. For children receiving treatment in Machiton and TB Paediatric Hospitals, the twice weekly sessions bring a ray of joy, lifting patients from what can sometimes be low moods. Counsellors engage the children in constructive play, providing a creative outlet

[1] *Typically, a regimen not initially including injections and where the patient is not suffering ongoing side effects. Regimens including SCR, new drugs and syrups permissible.*

that helps to stimulate the mind and imagination, as well as developing important motor skills and hand-eye coordination.

The concept is designed to not only provide positive and fun engagement for children, but with an important and valuable effect of supporting their development. In 2017, the PST ran a total of 121 play therapy sessions. In addition, MSF regularly hosts celebration events at both healthcare facilities. This is a day of celebration for programme patients who are on treatment and working their way towards a healthier future. It is a day for staff, caregivers and patients to come together, eat, dance, play games, sing, discuss their lives and share small gifts.

"We noticed kids are very adherent to treatment when there is a child-friendly surrounding. I am so grateful to have one like that in our hospital. Play-therapy with a teacher, nursery rhymes, mentally stimulating games; all these contribute to the continued education and well-being of a child during treatment."

Dr. Firuz Sharapov, medical director, Machiton TB Hospital

4.3.3 Nutritional support

Insufficient nutrition heightens vulnerability to TB infection. Children are among those most at risk of developing MDR-TB while TB itself can be a cause of chronic malnutrition (11). Malnutrition may impact the effectiveness of drug regimens, while at the same time mal-absorption of drugs due to associated diarrhoea can play a role in the development of MDR-TB.

This relationship between TB and malnutrition is evident in the programme's cohort as more than one third of all adults were classified as underweight, and a little over half of under 18-year-olds were suffering severe or moderate acute malnutrition at the start of their treatment (see results section). This is why the MoH/MSF programme supports improved nutrition in health facilities, directly providing nutritional support to all patients and caregivers in paediatric and Machiton hospitals.

For ambulatory patients on DOT and F-DOT programmes, the nutritional support is two-fold. Clinical criteria, such as patient history and anthropometric measures indicating BMI and z-score, determine if a patient needs supplementary food support. In these cases MoH/MSF provides food packs that include ready-to-use therapeutic food (RUTF), additional vitamins and minerals, and deworming treatment.

There are also a range of socio-economic criteria that may make a family eligible for additional supplementary food support, namely:

- Patient resides with a single caregiver
- Caregiver is unemployed
- There is more than one patient in the family
- There are five or more people living in the house

As part of the initial assessment, the programme social worker determines if additional nutritional support may be needed, and also tries to link family members to employment opportunities in partnership with the Department of Labour. Regular revisits and re-assessment track how the family are managing in response to fluctuating work and income, seasonal changes and other factors.

TACKLING CHALLENGES

Prioritising psycho-social care in resource limited settings:

Delivering truly patient-centred care goes beyond the clinical treatment of the disease and into the areas outlined above. Health education and counselling support make a tangible difference to patients and their families in terms of achieving adherence, coping with side effects and reducing transmission. But these activities need to be prioritised alongside clinical care.

Contexts like Tajikistan rarely have the luxury of specialist staff, nor the resources required to make counselling, play therapy and nutritional support standard parts of the patient-centred care package. A combination of high level leadership and collaborative partner support is needed to realise a widespread treatment model that goes beyond direct clinical care, to a holistic approach to patients and families.

5. Improving outcomes

5.1 Cohort description and main outcomes

Above all, the MoH/MSF programme aims to manage cases of paediatric MDR and XDR-TB to a successful outcome. Although challenging since its inception, the programme has never stagnated and always looks for innovative ways to provide better care. The programme does not exclude those with poor prognoses and it remains flexible to treat family members at risk, even if outside the target age range. New drugs and models of care are utilised alongside traditional approaches and ultimately, the successes are evident.

5.1.1 Cohort description

The MoH/MSF programme has collected demographic and clinical data on patients since the earliest days in 2011. To date, the total cohort comprises 232 cases. A small majority of the cohort are female (53.9%) and 42.2% of cases are under 15-years-old *(Figure 3)*. The median age is 15 for boys, 16 for girls.

Almost one quarter of the total cohort (23.9%) had extra-pulmonary TB mostly affecting the lymph nodes, although spinal, Potts disease and pleural effusion were also found among the cases. Six patients were HIV/TB co-infected at enrolment, four of whom were female. Total MDR cases represented 60.7 percent, XDR cases comprised 27.5 percent. The majority of others were pre-XDR, plus a small number of poly- and mono-resistant cases.

Based on WHO child growth standards, at treatment start 18.5 percent of the paediatric cases (<18 years) were categorised as having severe acute malnutrition (SAM) and an additional 34.0 percent with moderate acute malnutrition (MAM) (24). Over a third (38.3%) of total adult cases (18-years and over) were also underweight according to WHO BMI classification (25). This double-burden of TB and malnutrition is particularly alarmingly in children and demonstrates the crucial role the programme's early intervention with nutritional support plays *(Figure 4)*.

5.1.2. Contribution of contact tracing

Contact tracing has been an essential component in finding cases. A concerted effort since 2016 has yielded around 6,000 visits with family members and close contacts (initial and follow-up). This has resulted in detection and inclusion into the MoH/MSF cohort of 57 DR-TB patients, the majority paediatric but also some adult contacts.

These cases comprised 34 percent of those starting treatment in 2016, rising to 55.8 percent in 2017. By mid-year, programme eligible contacts detected had already accounted for over one third (37.0 %) of the 2018 cohort. Overall 43.9 percent were aged under 15 years, which is in-line with a study finding 39–50 percent of children estimated to develop MDR-TB each year could be identified through household contact tracing (6).

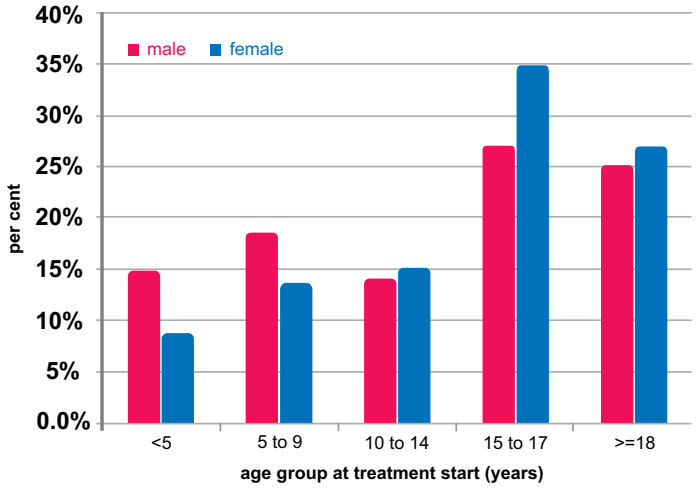


Figure 3. Age group distribution by sex, MoH/MSF Tajikistan Paediatric TB programme.

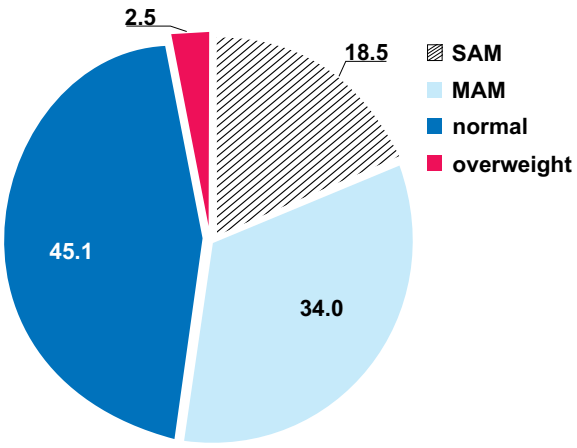


Figure 4. Proportion of paediatric (<18 years) cases categorised by WHO child growth standards, MoH/MSF Tajikistan Paediatric TB programme patients.

5.2 Results and outcomes

There has been a clear upward trend in the number of cases commencing treatment year on year. For the 147 cases with a treatment outcome, the impact of the programme is clear with 82.3 percent overall achieving successful outcomes (completed/cured). Unsuccessful outcomes include people who have died or failed treatment. Figure 5 below depicts the total number of patients starting treatment each year. The number of successful and unsuccessful outcomes shown are for those whose treatment ended in each respective year. As treatment can take up to two years, the total number of outcomes do not equal the number of people starting treatment in that year.

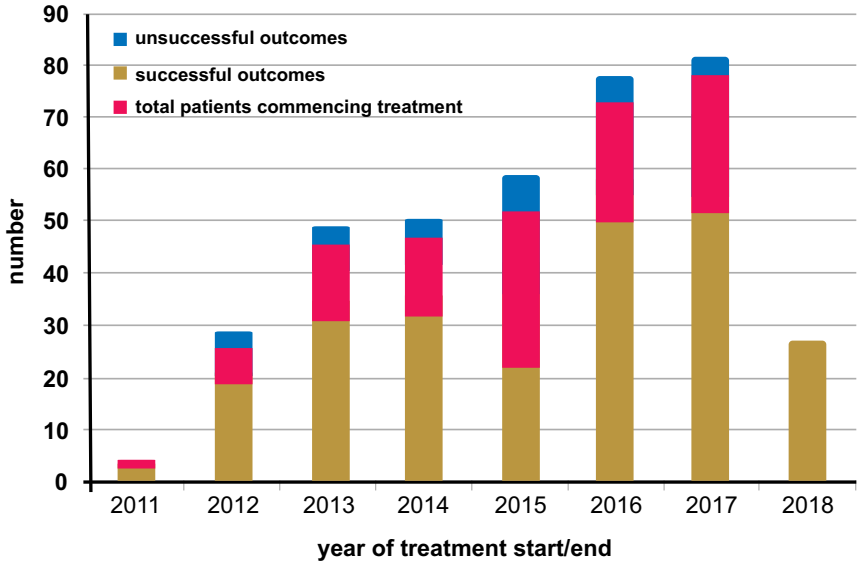


Figure 5. Number of cases (by treatment start year) and outcomes (by treatment end year), MoH/MSF Tajikistan Paediatric TB Programme, 2011-2018.

5.2.1 Empirical and individualised regimens

Where it is not possible to obtain sputum samples for DST testing, patients have to start treatment on an empirical basis and the regimen assigned based on patient history, clinical signs and the DST pattern of the adult contact. Contact tracing has been invaluable in better informing the composition of empirical regimens.

At the same time, the programme focus on sputum indication along with diagnostic tool advances, has meant that more patients year on year have started on individual regimens. It is a transition that can be seen over time *(Figure 6)* along with the notable increased inclusion of new drugs. Of those with recorded outcome and regimen type, individual regimens accounted for successful outcomes in 83.3 percent of XDR, 77.8 percent of new drug and 50.0 percent of MDR cases respectively.

5.2.2 New drugs and shortened regimens

Following the introduction of Bedaquiline in 2015 and Delamanid in 2016, the proportion of cases starting treatment on the new drugs has risen steadily, accounting for 66.7 percent so far in 2018. Part of this is driven by an increase in patients commencing injection-free regimens. At the same time those on SRC comprised 32.7 percent in 2017 and were already 30.8 percent by the mid-2018. There were 34 patients treated with Bedaquiline, 25 with Delamanid and eight with both. In total, 52 of the 67 patients treated with new drugs are off-label use; indicated by complying with any of the following criteria:

- Use exceeding 24 weeks – either drug
- Patient under 18-years-old (at start of taking drug) – Bedaquiline
- Patient under six-years-old (at start of taking drug) – Delamanid
- Patient taking both drugs at the same time

Numbers of those who have ended treatment after SCR or new drug regimens are still small, but the outcomes are very promising. SCR patients had successful outcomes in 81.8 percent of cases. All 10 Bedaquiline patients achieved a successful outcome, including seven who were off-label, one patient on combination regimen and one on Delamanid also achieved successful outcomes. Average off-label Bedaquiline

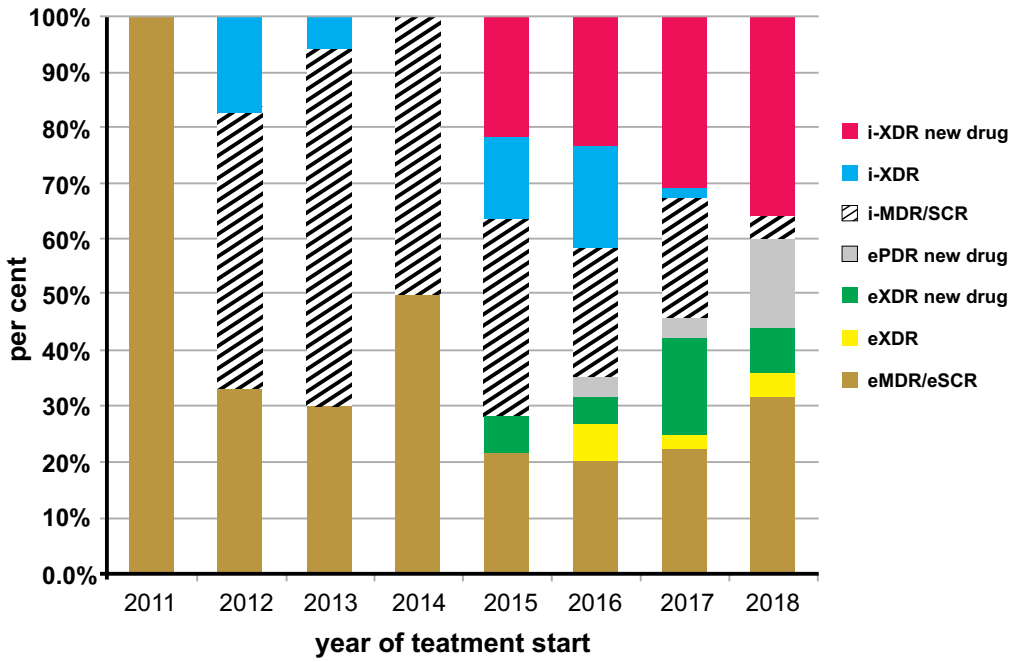


Figure 6. Proportion of regimen type, by year of starting treatment, MoH/MSF Tajikistan Paediatric TB Programme, 2011-2018.
** In the key 'e' denotes empirical regimen, 'i' denotes individual regimen. Excl. 2 PDR standard regimens in 2016.*

use was 28.9 weeks (95% CI. 25.6, 32.2) and 33.1 weeks (95% CI. 23.8, 42.4) for off-label Delamanid use among those completed and continuing the medication.

Treatment is ongoing for 84.6 percent of Delamanid, 70.6 percent of Bedaquiline and 87.5 percent of combination regimen patients, who are adhering and tolerating well. This encourages hope the programme will continue to demonstrate new drugs can be used successfully in regimens both on- and off-label, and in injection-free regimens for MDR- and XDR-TB.

5.2.3 F-DOT

A total of 11 patients from nine families have been enrolled in F-DOT to date. Of the 11 patients, all but two are aged under 15 years and a small majority (54.6 percent) are female. Six of the patients

Zukhro and her family: After the challenges of caring for two children in hospital, the family went on to complete treatment at home. Although difficulties remained, being on a SCR meant the children were cured much sooner and life returned to normal.

"After the fifth month we were discharged from hospital and continued the remaining four months of treatment at home. At the beginning, it was difficult for me to manage my kids' treatment; when they were taking drugs they would cry, they wouldn't want them, and I even noticed my son became more aggressive. Then I realised it was the environment – they were missing toys, big shady trees, mild air and playgrounds that used to be in hospital area. We didn't have those conditions at home to distract the children and help improve their low mood. But home is home and I can cook them their favourite meal anytime and they can play with other kids in the neighbourhood.

Now, I can see nine months of treatment is effective, the children are healthy and doing well. To see them cured was such a happy feeling. I was so glad that we could see the doctor in time and started treatment as early as possible. Now, I can see TB is curable.

Their granny, my husband and everyone else were happy that we took the right treatment on time, and that my children got back to the normal life they had before. It was a load off of my mind. I would like them to become doctors in the future, because I can already see they have an interest in it. When they play together they imitate doctors and patients, they enjoy it."

had XDR-TB, but none were HIV co-infected. Six were able to start ambulatory care from day one, while the five who started treatment in hospital have successfully managed the transition to a home-based model of care.

Five of the F-DOT patients' regimens include Delamanid and in all cases off-label (prolonged use beyond 24 weeks; one patient aged under six years). Four F-DOT patients were on the SCR MDR regimen, two who have now completed treatment. In total there were four successful outcomes for patients whose duration of F-DOT care ranged between 1.5 to 11.4 months.

"Despite the challenges of work, what helps me to stay motivated is my passion for this profession. . . and now, with all the innovations in this sphere, it becomes more and more interesting. In the future, I want to see MDR-TB doesn't exist at all, and that each aspect of TB care is fully implemented to react on time to prevent the disease."

Dr. Nigora Badridinova, TB doctor, Polyclinic 9, Dushanbe

6. Conclusion and recommendations

This MoH/MSF programme has unequivocally demonstrated it is feasible to successfully find, test and treat paediatric MDR-TB patients in Tajikistan. The results and lessons learned throughout implementation therefore lead to a range of conclusions and recommendations for any TB programme seeking to effectively tackle paediatric TB:

1. Conduct active case finding/contact tracing – Successfully addressing paediatric TB requires relevant health actors to actively find cases that may be 'hidden' due to a lack of symptoms, infection with latent TB, delayed health-seeking behaviours, a lack of health education, stigma or other reasons. Detect and intervene early where children are at risk and identify DR patterns of adult contacts where applicable. Use the opportunity to strengthen the education and training of local healthcare workers, as well as health education in the community and promoting infection control measures within the home.

2. Widen access to enhanced sample collection and diagnostic tools – Reduce time to diagnosis and base patient regimens on more detailed information. Provide child-friendly sample collection methods in tandem with best practice diagnostics that are reliably stocked and well distributed. Provide the most accurate way to confirm patients' DR patterns and start the right treatment faster.

3. Prescribe new drug and short course regimens wherever possible – Use new drugs Bedaquiline and Delamanid, which are increasingly shown to be effective and well-tolerated in both on and off-label use. The new WHO 2018 guidance further promotes the use of Bedaquiline in particular, while significantly deprioritising the use of injectable drugs. In the experience of the MoH/MSF project, Bedaquiline and Delamanid deliver equally successful outcomes as traditional regimens, as does the SCR, but in substantially less time.

4. Practice patient-centred care – Broaden the approach beyond only treating clinical needs within the framework of standard models of care – hospitalised intensive phase, DOT continuation phase. Practice a holistic approach that is flexible, adaptive and responsive to patient needs and includes greater use of ambulatory care from day one, and family-based care. Complement this with essential nutritional support, psycho-social care and health education.

5. Integrate TB and HIV services – Create pathways that bridge the gap between vertical TB and HIV systems which permit little cross-over of knowledge or patient management between the respective national programmes. Without the inclusion of HIV status in a TB patient's clinical history, co-infected TB patients are unlikely to be prescribed the optimum regimen. At the same time, HIV positive patients with undetected TB will contribute to the increasing case severity and transmission that all the above recommendations aim to halt.

6. Continue collaboration with partners at all levels – The MoH/MSF partnership has been successful in enabling Tajikistan to access skills and dedicated resource support to meet the challenges presented by paediatric TB. However, small scale discreet projects are not enough. Collaboration

at all levels is needed to achieve widespread implementation of practices and policies, reduction of resources gaps and scaling-up of activities to sustain the gains made to date, and to meet future challenges:

- **Local** – Healthcare facilities within the country should establish and foster collaborations that provide opportunities for training and knowledge transfer of in-country expertise. For example, Machiton hospital offers technical training, while 'train-the-trainer' cascade programmes are an efficient way to disseminate the skills needed to achieve widespread implementation of the guidelines. Improving communication between local partners, and within different levels of the healthcare sector, also helps identify gaps that could support NTP staff on the ground prioritise distribution of resources.
- **National and regional** – National programmes should adopt and adapt from regional examples, using regional forums to share expertise and technical support to strengthen key areas such as infection control, waste management, laboratory and psycho-social care capacity. International mechanisms such as the WHO collaborative procedures for accelerated registration should be leveraged by national governments, which must remain open to developing creative legislative remedies that may not require registration for certain drugs.
- **International** – National governments must continue to lobby the international community through existing mechanisms and forums to ensure paediatric DR-TB in moves up the global agenda. There is still much to do to mobilise funding, speed up diagnostic and drug development, improve equity of access to technology and to disseminate the mounting global best-practice evidence. From the other side, in the case of the Global Fund and Global Drug Facility for example, regulatory harmonization must be a two-way street - a shared commitment rather than top-down, imposed set of requirements. International actors must stand ready to match the increased political commitment demanded from national governments.

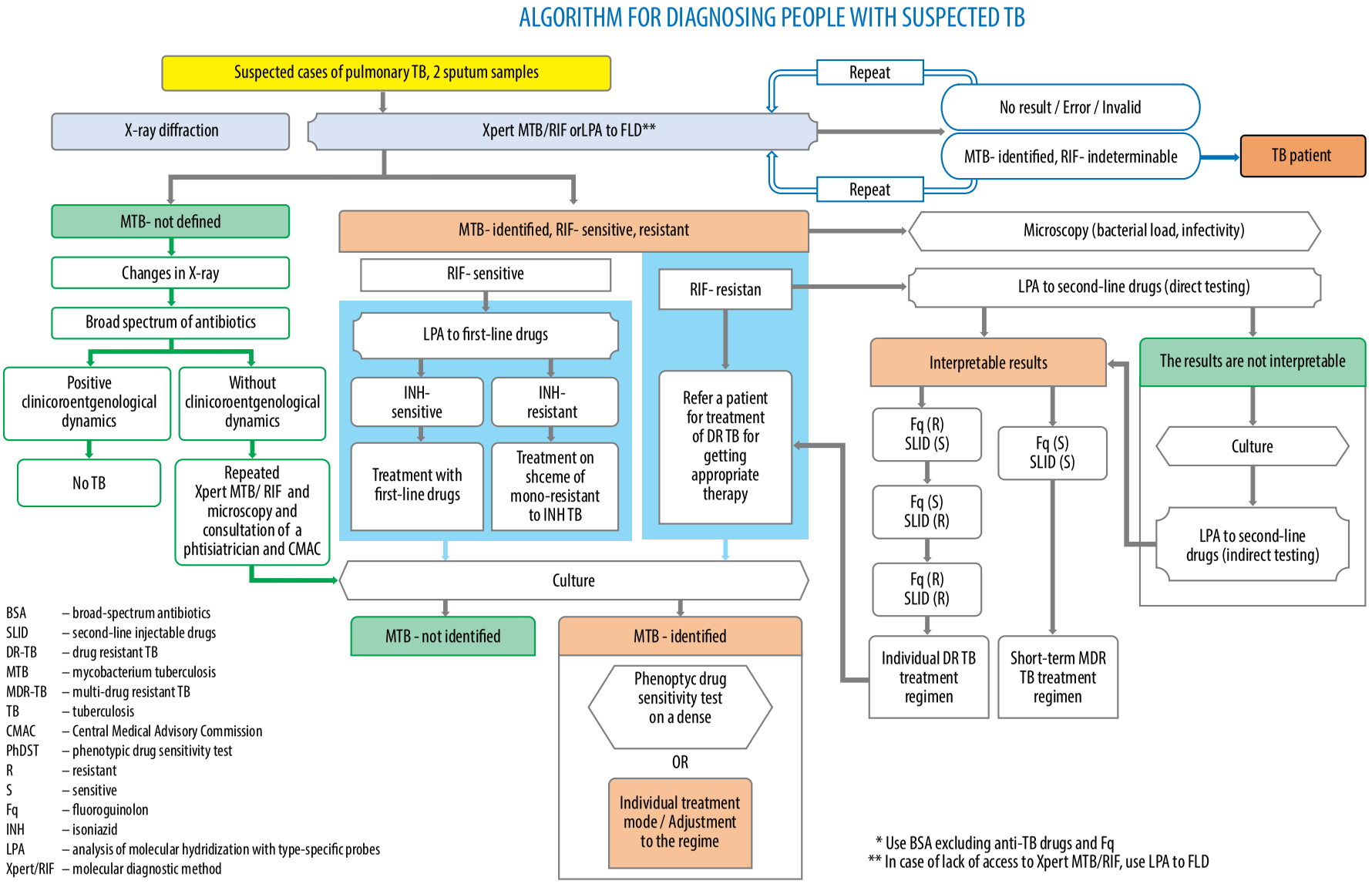
Tackling paediatric TB remains challenging, but the advances made show that innovation and ambition are rewarded with significant steps forward. These recommendations are not mutually exclusive and should be considered as additive; producing amplified impact with implementation of each respective measure. Families in this programme have shown they are willing to embrace innovative treatments and models of care in pursuit of a cure for their child. National programmes and leaders in Government must show equal bravery and commitment for the sake of all children that are, or could be, affected by TB.

BIBLIOGRAPHY

1. World Health Organization. The End TB Strategy. 2014.
2. World Health Organization. Global tuberculosis report 2017 2018.
3. World Health Organization. The global MDR-TB & XDR-TB response plan 2007-2008. 2007.
4. World Health Organization. Childhood TB 2018 [cited 2018 22 August]. Available from: www.who.int/tb/areas-of-work/children/en/.
5. World Health Organization. Roadmap for childhood tuberculosis: towards zero deaths. Geneva: WHO. 2013.
6. Jenkins H, Yuen C. The burden of multidrug-resistant tuberculosis in children. The International Journal of Tuberculosis and Lung Disease. 2018;22(5):S3-S6.
7. World Health Organization. Use of high burden country lists for TB by WHO in the post-2015 era. Geneva: World Health Organization. 2015.
8. Ministry of Health and Social Protection of Population, Republic of Tajikistan. National Investigation of Drug-Resistance in the Republic of Tajikistan (divided by Regions) 2016-2017. 2018.
9. World Health Organization. WHO Country Profile Report Tajikistan 2017 [cited 2018 21 August]. Available from: https://extranet.who.int/sree/Reports?op=Replet&name=%2FWHO_HQ_Reports%2FG2%2FPROD%2FEXT%2FTBCountryProfile&ISO2=TJ&LAN=EN&outtype=html.
10. World Health Organization. Global strategy and targets for tuberculosis prevention, care and control after 2015. World Health Organization; 2013.
11. Schaaf HS, Marais BJ. Management of multidrug-resistant tuberculosis in children: a survival guide for paediatricians. Paediatric respiratory reviews. 2011;12(1):31-8.
12. Mirtskhulava V, Kempker R, Shields KL, Leonard MK, Tsertsvadze T, del Rio C, et al. Prevalence and risk factors for latent tuberculosis infection among health care workers in Georgia. Int J Tuberc Lung Dis. 2008;12(5):513-9.
13. World Health Organization. WHO policy on TB infection control in health-care facilities, congregate settings and households. Geneva: World Health Organization. 2009.
14. World Health Organization. Latent tuberculosis infection: updated and consolidated guidelines for programmatic management. 2018.
15. Schaaf HS, Garcia-Prats AJ, McKenna L, Seddon JA. Challenges of using new and repurposed drugs for the treatment of multidrug-resistant tuberculosis in children. Expert review of clinical pharmacology. 2018;11(3):233-44.
16. Fitzpatrick MC, Floyd K. A systematic review of the cost and cost effectiveness of treatment for multidrug-resistant tuberculosis. Pharmacoeconomics. 2012;30(1):63-80.
17. World Health Organization. MDR-TB surveillance 2015 [cited 2016 21 Aug]. Available from: http://www.who.int/tb/areas-of-work/monitoring-evaluation/mdr-tb-surveillance/en/.
18. Ködmön C, van den Boom M, Zucs P, van der Werf MJ. Childhood multidrug-resistant tuberculosis in the European Union and European Economic Area: an analysis of tuberculosis surveillance data from 2007 to 2015. Eurosurveillance. 2017;22(47).
19. Medecins Sans Frontieres Access & STOP TB Partnership. Out of Step in EECA: TB Policies in 8 countries in Eastern Europe and Central Asia.; Nov 2017.
20. World Health Organization. Rapid Communication: Key changes to treatment of multidrug- and rifampicin-resistant tuberculosis. 2018.
21. Ministry of Health and Social Protection of Population, Republic of Tajikistan. The Guidance for the Diagnosis and Treatment of Tuberculosis in Children of the Republic of Tajikistan, 3rd revised Edition.; 2017.
22. Kim S, Seddon J, Garcia-Prats A, Montepiedra G. Statistical considerations for pediatric multidrug-resistant tuberculosis efficacy trials. The International Journal of Tuberculosis and Lung Disease. 2018;22(5):S34-S9.
23. Garcia-Prats A, Svensson E, Weld E, Schaaf H, Hesseling A. Current status of pharmacokinetic and safety studies of multidrug-resistant tuberculosis treatment in children. The International Journal of Tuberculosis and Lung Disease. 2018;22(5):S15-S23.
24. World Health Organization. WHO Global Database on Child Growth and Malnutrition 2018 [cited 2018 15 June]. Available from: http://www.who.int/nutgrowthdb/about/introduction/en/index5.html.
25. World Health Organization. WHO Global Database on Body Mass Index 2018 [cited 2018 15 Jun]. Available from: http://apps.who.int/bmi/index.jsp?introPage=intro_3.html.

ANNEX A FIGURE A

Diagnostic algorithm for confirmation of TB in Tajikistan, Republican Centre for Protection of Population from Tuberculosis, March 2018



PDTB Report, v4 as at 26 Sept 2018

ANNEX A TABLE A

Table 1. Key features of anti-TB drugs in use in MoH/MSF Tajikistan Paediatric TB Programme patients, 2018

Drug name (abbrv.)	Paediatric formula	Adverse events noted in MoH/ MSF cohort	FDOT use	Age / weight restrictions	Availability	Effectiveness*
Isoniazid (high) (HH)	Yes	hepatic disorders, hypersensitivity	Yes	No	widespread	high\low
Ethambutol (E)	Yes	None noted	Yes	No	widespread	low
Pyrazinamide (Z)	Yes, upcoming new formula	arthralgia, hepatic disorders, gastrointestinal disturbances	Yes	No	widespread	medium
Kanamycin (Kn)	Yes	nephrotoxicity, hearing loss, electrolyte disturbances, local pain at injection site	No	No	widespread	medium
Capreomycin (Cm)	Yes	electrolyte disturbances, nephrotoxicity, hearing loss, local pain at injection site	No	No	limited	medium
Levofloxacin (Lfx)	Compounding compatible, upcoming new formula	gastrointestinal disturbances, headache, CNS disorders (dizziness, insomnia, depression, myalgia, QT prolongation)	Yes	No	widespread	high
Moxifloxacin (Mfx)	Compounding compatible, upcoming new formula	gastrointestinal disturbances, headache, myalgia	Yes	No	limited	high

Drug name (abbrv.)	Paediatric formula	Adverse events noted in MoH/ MSF cohort	FDOT use	Age / weight restrictions	Availability	Effectiveness*
Prothionamide (Pto)	Compounding compatible, upcoming new formula on ethionamide	Nausea, vomiting diarrhoea, metallic taste in mouth, endocrine disorders, hepatitis	Yes	No	widespread	medium
Cycloserine (Cs)	Compounding compatible, upcoming new formula	Personality change, dizziness, depression	Yes	No	widespread	medium
Para-aminosalicylic Acid (PAS)	Yes	Nausea, vomiting, gastritis, diarrhoea, hypothyroidism, hepatitis	Yes	No	widespread	low
Chlofazimine (Cfz)	Compounding compatible, upcoming new formula	Gastrointestinal disturbances: nausea, vomiting, abdominal pain, diarrhoea, pink, red or brownish discolouration of skin, body fluids and faeces, eye and skin dryness and irritation	Yes	No	limited	high
Linezolid (Lzd)	Commercially prepared syrup available	Anaemia	Yes	No	limited	high
Delamanid (Dlm)	Yes (off label <6 years)	QT prolongation	Yes	Yes (off label <6 yrs old, <20kg)	limited	high
Bedaquiline (Bdq)	No (off label)	Nausea, arthralgia, headache, hepatitis, QT prolongation	Yes	Yes (off label <18 yrs old, <33kg)	limited	high
Imipenem / Cilastatin (Imp) *administered together with*	Yes	None noted	No		limited	medium
Amoxicilin / Clavulanate (Amx/Clv)	Yes	Diarrhoea	No		widespread	low

** assumes patient not resistant*

MEDECINS
SANS FRONTIERES

Address: 5/3 Bukhoro Str.,
Dushanbe 734025, Tadjikistan

Phone number: +992 37 224-51-50
http://www.ru.msf.org