TB REACH WAVE 9

Addressing inequities in drug-resistant tuberculosis under the principles of USAID Global Accelerator to END TB and UN HLM on TB.

DR-TB Technical Brief

Wave 9 of TB REACH is specifically focused on addressing drug-resistant tuberculosis (DR-TB), including rifampicin-resistant (RR), multidrug-resistant (MDR), and extensively drug-resistant (XDR) tuberculosis (TB), for both children and adults.

Applications will be accepted for the following three categories of activities:

1. Linkage to care to reduce pre-treatment loss to follow up (LTFU) for DR-TB.
2. Implementation of all oral DR-TB treatment regimens.
3. Improving treatment adherence and outcomes.

Global Background and Context

In September 2018, the United Nations General Assembly High-Level Meeting (UNHLM) on TB set the stage for high-level attention and action on TB. This meeting established the ambitious target of diagnosing and enrolling an additional 40 million people on TB treatment by 2022 (commonly referred to as 40x22), which includes detection and enrollment of treatment of 1.5 million people with DR-TB. To help countries achieve these targets, at the 2018 UNHLM, United States Agency for International Development (USAID) Administrator Mark Green announced the Agency's new TB business model – the Global Accelerator to End Tuberculosis as well as Journey to Self-Reliance.

1. Linkage to care to reduce pre-treatment loss to follow up for DR-TB.

According to the World Health Organization (WHO) TB data released in late 2020, there were an estimated 465,000 (range, 400 000–535 000) incident cases of MDR/RR-TB in 2019. However, only 206,030 (44.3%) cases of DR/RR-TB were detected and notified in 2019, representing a 10% increase from 186,883 in 2018. While the DR-TB case finding is far below the total estimated cases, and the annual increase is lower than anticipated, the number of people initiating treatment was even lower. In 2019, only 177,099 (86%) persons detected with DR-TB initiated second-line DR-TB treatment. This means that one in every seventh of people diagnosed with DR-TB was not enrolled in treatment and likely will not be enrolled in the future. The progress on DR-TB treatment initiation has been deteriorating over the last several years. In 2015, for example, among 132,120 people with DR-TB detected, 124,990 were enrolled on appropriate treatment, 94.6% of those detected. With the scale-up of rapid drug susceptibility testing (DST) and GeneXpert testing among new and retreatment cases over the last few years, more people have been detected with DR-TB, however, the capacity to enroll and sustain people on treatment has not kept the same pace, and as a result, the gap between the number of people detected and initiated on treatment is increasing.

Below are examples of activities of DR-TB programs that could be improved to reduce treatment initiation gaps:

- **Expanding the number of DR-TB treatment sites.** In many countries, a limited number of treatment centers are certified and assigned for DR-TB treatment initiation. While for drug-susceptible TB (DS-TB), most of the primary healthcare facilities can initiate and provide TB treatment, sometimes only specialized facilities can provide DR-TB care. This approach is based on the view that treatment adherence and management of adverse drug reactions may be only organized in hospitals or in selected facilities than in the community. With the roll-out of the all-oral short DR-TB treatment options, all TB facilities can be part of the DR-TB network.
- **Building human resources capacity and technical expertise.** Since the beginning of the DOTS Plus program, the management of DR-TB was considered very complicated and required special and unique training and professional experience to manage DR-TB. With the roll-out of all-oral regimens, implementation of shorter treatments, and reduction of medications to treat DR-TB, more providers can tackle the management of people with DR-TB. Activities aimed at bringing new providers into the DR-TB network,

build the capacity of current and new providers to manage DR-TB, and establish access to training and expert clinical consultation might help improve the initial LTFU.

- **Connectivity solutions for linking laboratory results to treatment.** While the use of GeneXpert testing has expanded greatly over the last 10 years, many testing sites are still far away from local health facilities. Reporting results of tests in a timely fashion has been a challenge in many settings. Connectivity solutions may be able to improve the linkages between testing and treatment initiation by ensuring that both the person with DR-TB and the health care workers know the results of the tests, and can make the appropriate referrals and connections to care.
- **Other activities may include but are not limited to what is listed below. There are numerous other activities that might help to address the issue and all ideas will be considered for TB REACH funding if they will improve the linkages to DR-TB care.**
  - Linking DR-TB diagnosis with appropriate care
  - Bringing treatment initiation close to people with DR-TB
  - Improving advocacy and communication at the community level in order to improve acceptance of DR-TB care
  - Etc.

2. Implementation of all oral DR-TB treatment regimens

Since 1997, WHO has been recommending treatment options for people with MDR-TB via a mixture of first- and second-line medications. Initial regimens contained both injectable and oral medications consisted of 5-7 drugs and lasted for 18-20 months.

In 2005, a 9-month treatment regimen (9MTR) was developed and tested in Bangladesh, with support from the Damien Foundation and the results published in 2010 by Van Deun et al. Later, several countries initiated pilot implementation of 9MTR under operational research conditions. In May 2016, WHO reviewed evidence from 9MTR regimen implementation in 20 countries and issued a 2016 update to the MDR-TB treatment guidelines, specifically recommending the implementation of the standard shorter regimen under programmatic conditions. In November 2018, WHO issued new treatment guidelines describing the following treatment options for MDR-TB: an all-oral treatment regimen with bedaquiline (BDQ), linezolid (LZD), and other second-line medications for a duration of 20 months, and a shorter standard treatment regimen for 9 to 12 months, containing first- and second-line medications and injectable medication. In November 2019, WHO issued a new Rapid Communication and updated its DR-TB Treatment Guidelines. WHO recommended a standard shorter, all-oral, bedaquiline-containing regimen for eligible individuals with MDR/RR-TB. The evidence and data analysis demonstrated that among individuals with FQ-susceptible MDR/RR-TB a shorter, all-oral, bedaquiline-containing regimen may be used instead of the standardized shorter regimen with an injectable. WHO recommended using the standard regimen lasting 9-12 months consisting of 4-6 months Bdq*-Lfx/Mfx-Eto-E-Z-Hh-Cfz / 5 months Lfx/Mfx-Cfz-Z-E (*BDQ is given for 6 months).

As described above, significant changes have been implemented in the DR-TB regimen design and duration since the beginning of programmatic management of DR-TB in 1997 and many countries struggle to keep up with the changes as they imply new drug procurement, new guideline development, training, sensitization, and capacity building, etc. Currently, all people with DR-TB can benefit from all-oral regimens, either 9-11 months in duration (for those without resistance to fluoroquinolones – FQ) or 18-20 months for individuals with FQ-resistance.

While many countries have accepted the recent changes in the DR-TB Guidelines and began the rolling out of new treatment regimens, the number of people receiving the latest recommended regimens are still small. Several countries are still reporting the use of injectable agents and/or implementation of longer treatment for those with FQ-sensitive TB.

Proposals under the Wave 9 applying under this category will propose innovative and scalable solutions that address the low uptake of novel DR-TB treatment regimens under programmatic conditions. Note that operational research proposals are not accepted. Only proposals that will use the new regimens under programmatic conditions will be considered. Below are a few examples of potential activities, which might help the country to initiate or scale-up novel regimens:

● **Catalyzing civil society, persons with DR-TB, and families to demand better treatment options.** Rapid changes in DR-TB treatment guidelines and practices creating cumbersome information environments for civil society members, persons with DR-TB, and their families. Multiple treatment changes and options presented at the international arena do not quickly trickle down to the level of a treatment facility in the country and are often implemented very slowly. Informing and consolidating civil society to work with the NTP to quickly adopt new treatment changes and then scale them up might help people with DR-TB to access better and safer care.

● **Engaging private providers in delivering novel treatment options.** While private providers are getting more engaged in TB case finding and sometimes in delivering TB care for people with DS-TB, they are often not immersed in DR-TB treatment. Establishing new partnerships with the private providers, helping them to get engaged in DR-TB care might help the country to scale up the treatment capacity and also adopt novel treatment options.

● **Expansion of DR-TB treatment sites.** It often takes time for TB treatment changes to be fully implemented across the country at the same speed. Facilities based in the country capital are often better positioned to adopt new guidance, while remotely based are last to implement the changes. Introducing novel regimens in remote, hard to reach TB sites or in specific populations might help countries to quickly scale up DR-TB regimens. Expanding the number of treatment sites across the country will allow the quicker roll-out of new treatment regimens and increase the number of people receiving novel regimens.

● **Other activities may include what is listed below, but not limited to. There are numerous other activities that might help to address the issue. TB REACH will accept all proposals that seek to improve the numbers of people receiving all oral novel regimens.**

- Digital technology aimed at assisting with the regimen design
- Solutions to tackle gaps in second-line drug supply and management in rural areas
- Distant clinical consultations, etc.

3. Improving treatment adherence and outcomes.

Quality of DR-TB care has always been a challenging issue for many TB programs globally. According to the 2020 WHO report, only 57% of people with MDR-TB successfully finished the treatment, while for those with DR-TB and also with FQ-resistance such results are even worse – 47%. Many National TB Programs (NTPs) and donors have been implementing activities to improve treatment adherence and quality of care overall in the last several years, however, it is still unacceptable and only improved minimally, from 52% reported in 2015.

Not only daily treatment adherence and final treatment outcomes are measurable indicators of treatment quality for DR-TB. Implementation of activities related to the detection and management of adverse drug reactions as well as out-of-pocket cost spent on TB detection and care also characterize program quality. In order to improve quality of care, NTPs need to roll out clinical and non-clinical components of DR-TB care, such as:

- Implementation of aDSM for all people with DR-TB, including children
- Implementation of people-centered approaches
- Delivering Care Package to all people in need
- Scaling up digital technologies for treatment support and monitoring
- Introducing palliative care for people in need

Below are a few examples of activities, which might help NTPs to achieve better treatment outcome with Wave 9 funding:

● **Providing support to encourage staying enrolled in care.** Although official guidance is minimal, there are many studies that have shown providing nutritional, emotional, and/or financial support to people with DR-TB and their families can have a positive effect on treatment outcomes and on costs. Proposals that target bottlenecks in the system through the provision of different support services to people with DR-TB are welcomed.

● **Implement digital adherence technologies.** The use of digital adherence technologies (DATs) is on the rise for TB care and could play an important role in assisting NTPs and people receiving care with treatment monitoring, counseling, reporting adverse drug reactions, etc. Wave 9 funds could be utilized to support the development or piloting of already existing tools and the adaptation

of them to country needs and settings; scaling up if already in place, etc.

- **Piloting delivery of non-clinical services via NGO support.** TB care delivery and especially the DR-TB one is often considered a very medicalized intervention and performed by the NTP staff. However, there are a number of essential components in DR-TB care, which are non-clinical and can be delivered by the local non-governmental organizations (NGOs). NGOs can partner with persons with DR TB, family members, caregivers and members of communities, and special interest groups to develop interventions around health-promoting behaviors and to strengthen skills and resources that will allow people to take control of their treatment.
- **Supporting advocacy movements.** Local NGOs and civil society organizations could play an important role in collecting and presenting issues, which people with DR TB are facing during DR-TB treatment. Persons with DR TB's experience, issues faced during the treatment, and gaps in delivering quality care can be presented at the national level so that NTP and the donor community pay more attention and implement corrective actions and deploy appropriate solutions.
- **Other activities (there are numerous other activities that might help to address the issue and the examples here are not meant to be prescriptive. TB REACH will accept all proposals that seek to improve DR-TB outcomes):**
  - Partnering with local governments to scale up treatment at home programs and non-medical support
  - Engaging private providers to help people with DR-TB stay adherent to treatment
  - Partnering with large businesses to help employees get appropriate DR-TB care and support, etc.

References

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