JOURNEY TO THE IMPLEMENTATION OF NEW DRUGS AND REGIMENS: CHALLENGE TB EXPERIENCE

INTRODUCTION

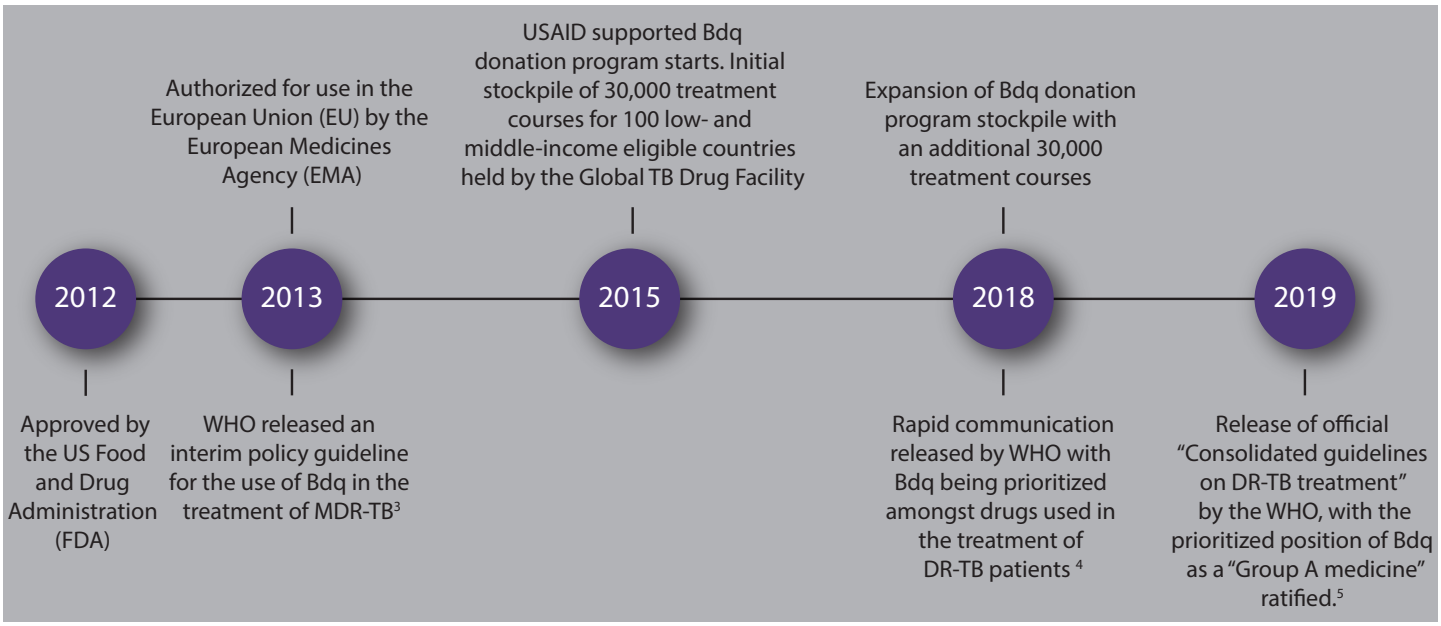
In 2017, it was estimated that there were approximately 558,000 people suffering from rifampicin resistant (RR-)/multidrug-resistant TB (MDR-TB).[1] MDR-TB is a public health crisis as it is more difficult to diagnose, its treatment is more expensive and longer (up to 24 months), and the drugs can have severe side effects, some of them permanent. Worldwide, only 55 percent of MDR-TB patients were treated successfully and in 2017, there were about 230,000 deaths from MDR/RR-TB.[1]

Bedaquiline (Box 1) and delamanid (Box 2) became the first two new drugs approved by regulatory authorities for the treatment of TB – currently recommended for use in the treatment of RR-/MDR-TB.

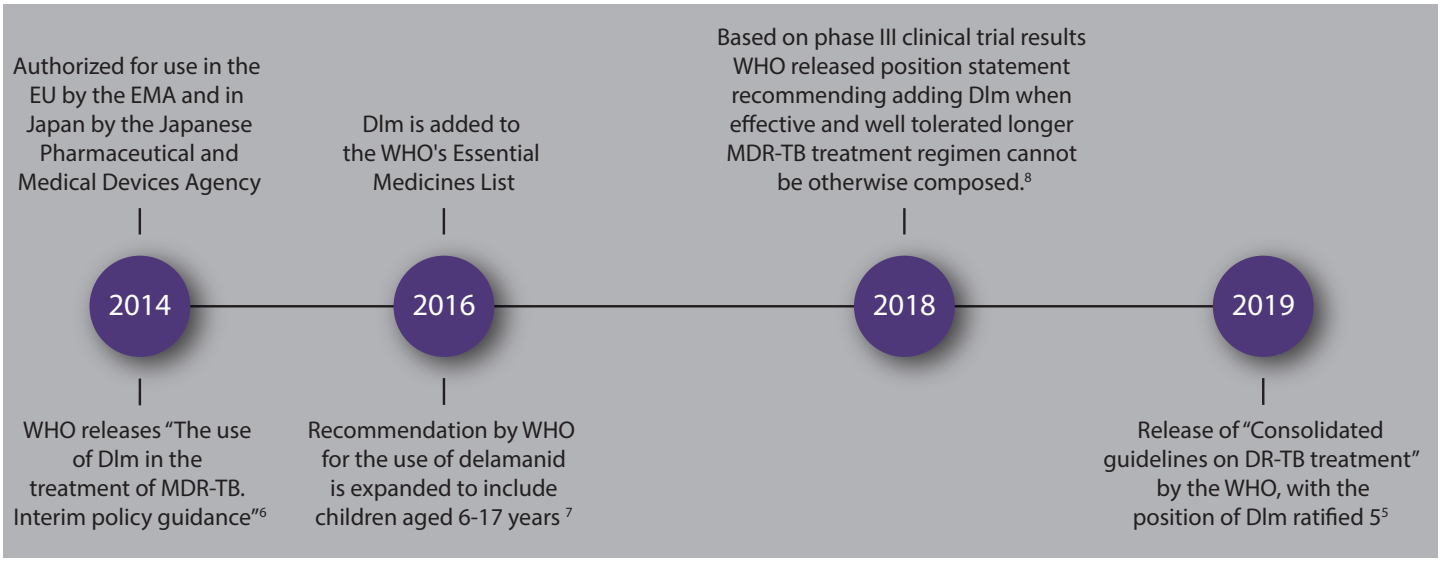
The introduction brought hope to patients worldwide suffering from drug resistant TB (DR-TB), including its most complicated variant extensively drug resistant TB (XDR-TB), that have limited treatment options.

The standardized shorter treatment regimen (STR – Box 3), as its name implies, is a shorter course of treatment that can be completed in 9-11 months (as compared to 18 to 24 months) for the treatment of RR-/MDR-TB. The STR was recommended by the World Health Organization (WHO) in 2016.[2] The STR provides a clear advantage for patients and the health system, by decreasing the length and cost of treatment.

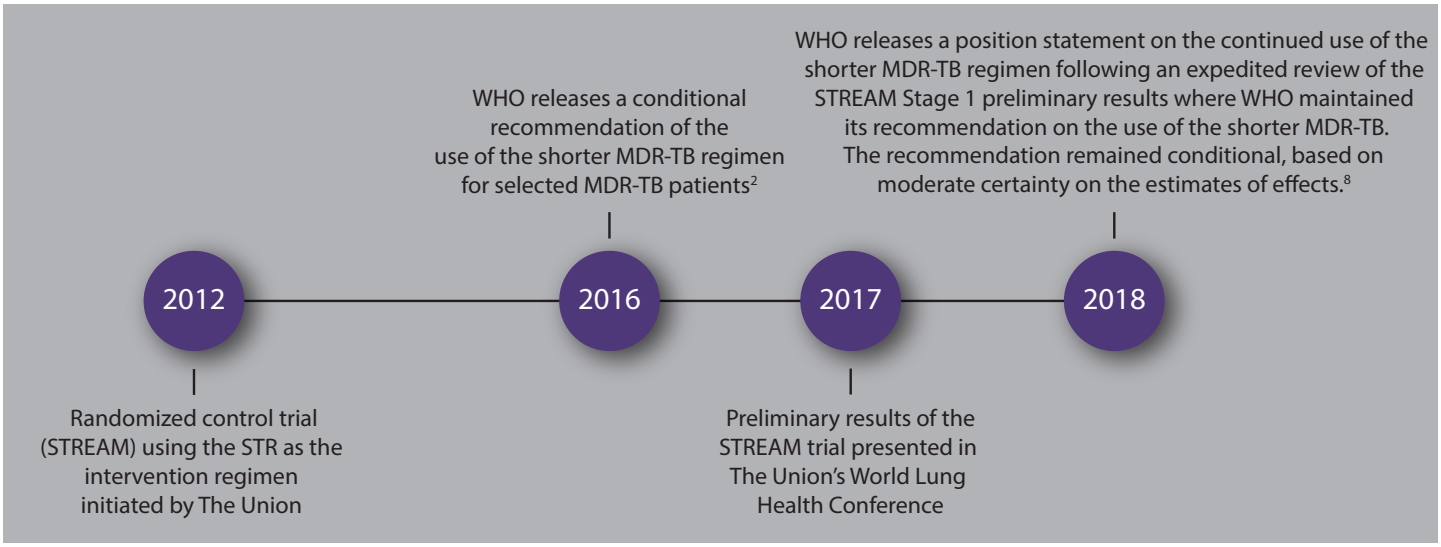
Box 1: Bedaquiline (Bdq) - First new TB drug for over 40 years. Developed by Janssen Pharmaceuticals (parent company Johnson & Johnson)



Box 2: Delamanid (Dlm) - Second new TB drug in over 40 years. Developed by Otsuka Pharmaceutical



Box 3: Shorter RR-/MDR-TB regimen (STR)

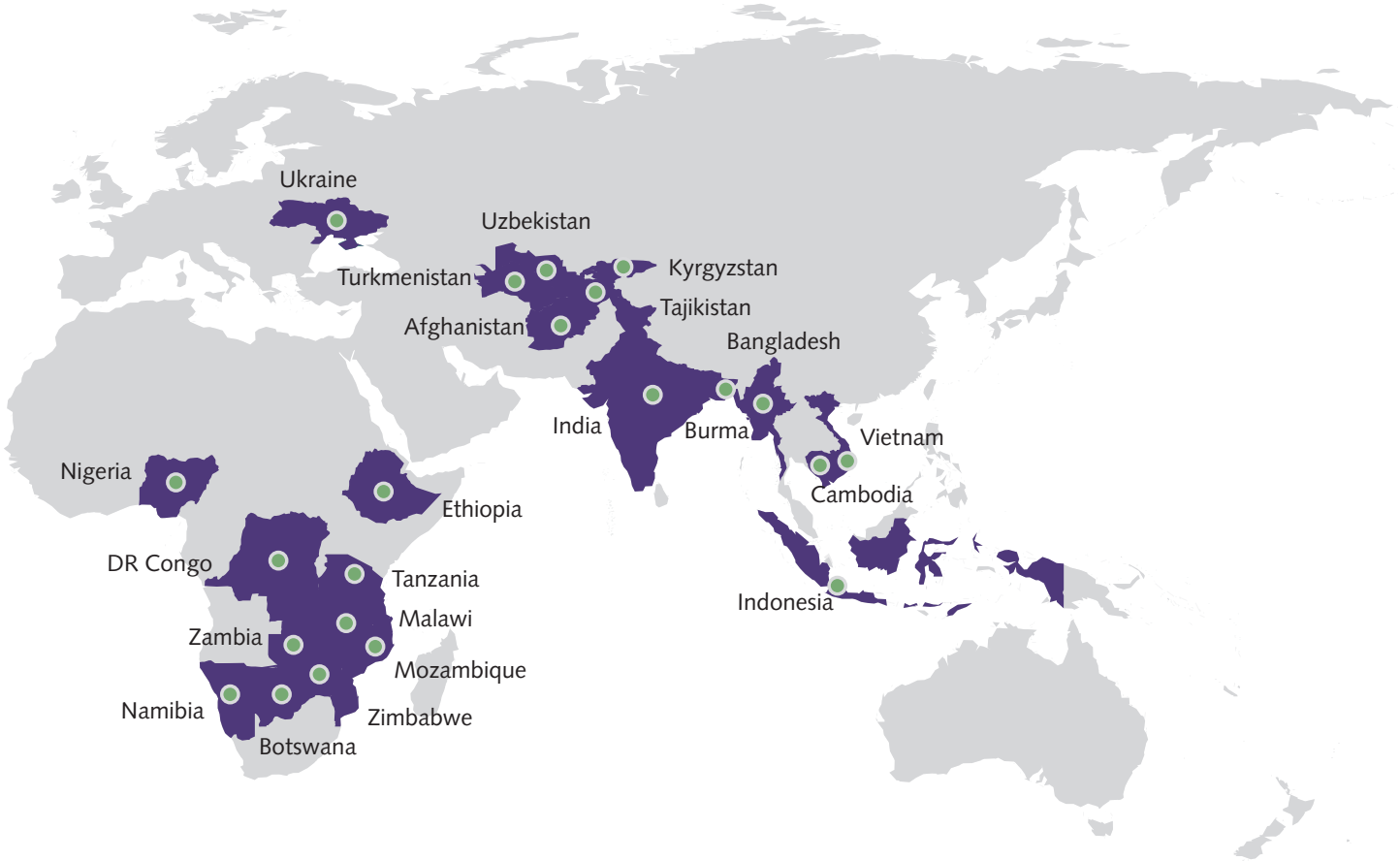


SITUATION

CTB supported the programmatic introduction of ND&R in 23 countries (Figure 1). These countries are amongst those included in one or more of WHO's high-burden country lists for TB, TB/HIV, and MDR-TB. Although they have very different geographical, cultural and epidemiological profiles and specific situations vary, there were common problems and challenges, among them:

- Very low treatment success rate amongst patients with more extensive drug resistant form of TB (below 35%).[1]
- The introduction of rapid molecular tests for the diagnosis of TB and RR-TB increased the number of RR-TB cases diagnosed worldwide. Thus there was a need to expand the number of sites providing MDR-TB treatment to keep up with this increasing diagnosis.
- Bedaquiline, delamanid and the shorter regimen, were the first 'new drugs and regimens' (ND&R) introduced in countries in many years, therefore most National TB Programs (NTPs) did not have previous experience in introducing the drugs in a programmatic manner. Although in some selected countries ND&R were already being used, they were being provided to a small number of patients under compassionate use and were restricted to either research facilities or international NGOs.
- NTPs were not used to coordinate with drug regulatory agencies, the latter being the ones responsible for accepting the widespread use of the ND&R on the countries. This was one of the principal challenges to be overcome before programmatic introduction was possible.
- The introduction of ND&R, as per WHO recommendations had to come with greater need for monitoring drug safety under pharmacovigilance systems. This was an area where most countries had severe shortcomings as access to monitoring tests and reporting mechanisms were either not in place or not being used.
- The quantification of drugs needed and the procurement of drugs for treatment of MDR-TB were not robust.

Figure 1. The Challenge TB project: 23 countries



IMPACT OF THE INTERVENTION

CTB focused on increasing the treatment coverage of RR-/MDR-TB and improving the quality of DR-TB management, and actively helping countries to plan, implement, and introduce the new TB drugs (Bdq, Dlm) and regimens (the STR), with the aim of improving the treatment outcomes of patients and reducing the treatment gap, thus ensuring that every patient has access to the treatment they need and that no MDR-TB patient goes untreated. Tackling the above mentioned issues not only aims to help patients but also to reduce the risks that MDR-TB spread and further development of resistance poses to public health.

INTERVENTION

First and foremost, the programmatic implementation of ND&R required the support of multiple stakeholders at the country level and their coordinated actions. The implementation of ND&R was phased, initially in a few "pilot" treatment sites. These pilot sites helped gather evidence and helped improve the treatment model. Thus the lessons learned at these initial sites, were already incorporated in a refined model prior to the implementation of countrywide expansion.

Implementation planning tool

CTB developed an "Implementation Planning Tool" aiming at assisting countries in creating a step-wise approach for the programmatic introduction of ND&R. The tool encompassed all the necessary steps for the programmatic introduction of ND&R, ranging from gathering political support, adaptation of national strategic plans, selection and preparation of sites where the ND&R would first be rolled-out, enrollment of patients, and the required monitoring and evaluation. The tool helped select the first treatment sites in the country - these were selected based on their capacity to diagnose and appropriately follow-up patients, as well as the presence of qualified staff.

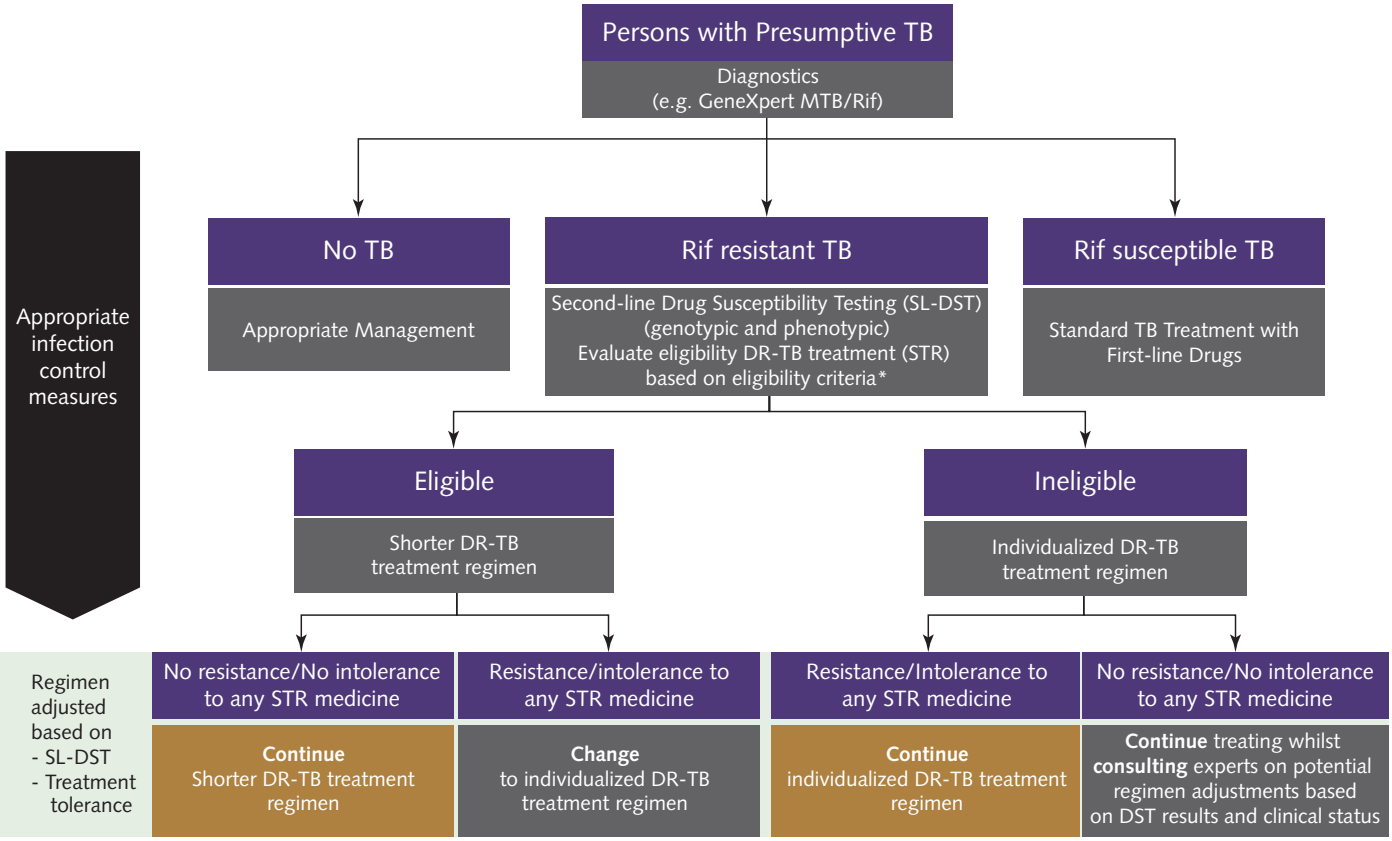
Policymaking, update of national guidelines, and creation of country expert groups

CTB provided technical support for the update of the national guidelines and with the implementation of the "right diagnosis, right treatment" approach which consists of a triage, where patients are screened and allocated a treatment that will best suit their needs based on drug-susceptibility testing (DST) results, their risk of resistance to second-line drugs (SLDs), the extent of their disease, HIV serological status, and pregnancy (Figure 2).

Once triaged, patients are either allocated to receive the STR or an individualized treatment regimen (ITR) either containing Bdq and/or Dlm. CTB staff joined national technical working groups (TB and MDR-TB TWGs), thus working from within to update all the required policies and guidelines. For the new drugs and regimens to be "legally" used in many countries, they first had to be part of national policy and included in national guidelines. In addition to the policy documents and technical guidelines, the project supported NTPs to develop SOPs, training materials, job aids, reporting forms.

In the CAR countries and Ukraine, CTB strengthened the existing expert groups (termed "Conciliums"), and in other countries, CTB helped NTPs to establish and run such expert groups. The concilium is a group of medical experts who confer and give advice, in this specific case, which patients could benefit from treatment with ND&R. Patients deemed eligible by physicians, were reviewed by the concilium who would decide whether the patient could benefit from treatment with an ITR containing Bdq and/or Dlm.

Figure 2. Patient Triage Approach



* Not eligible for the shorter treatment regimen are patients having 1) Resistance or suspected ineffectiveness to a medicine in the shorter MDR-TB regimen (except isoniazid resistance); 2) Exposure to one or more second-line medicines in the regimen >1 month (unless susceptibility to these medicines is confirmed); 3) Intolerance to any medicine in the shorter MDR-TB regimen or risk of toxicity (e.g. drug-drug interactions); 4) Pregnancy; 5) Disseminated, meningeal or central nervous system TB; or any extra-pulmonary disease in an HIV patient.

REGISTRATION OF DRUGS AND QUANTIFICATION OF NEEDS

In order for a drug to be used in a country, it has to be registered and its use authorized by national regulatory authority (NRA), once the NRA has considered the evidence of the medicine's safety, quality and efficacy. Bedaquiline and delamanid had to be registered for the first time in CTB countries and certain drugs in the STR (e.g. clofazimine) had to be registered for a new use (before it was authorized for use in patients with leprosy). CTB assisted in the registration of the drugs in some countries and helped secure waivers for importation of the respective drugs in other countries. Other countries only allowed the drugs to be used in research institutes until the registration process was completed.

Quantification of drugs needs were done based on the number of sites and number of expected patients for each regimen. In some countries a supply chain management specialist was embedded in the ministry of health full time to support NTPs in the quantification of drugs needs, creation of orders and plans for in country distribution. Technical assistance was also provided in the introduction and use of drug quantification tools, where possible in collaboration with the Global TB Drug Facility.

CAPACITY BUILDING OF MEDICAL STAFF

CTB supported numerous trainings of clinicians and health care personnel on ND&R. International experts also provided short term technical assistance (STTA) when needed. In order to streamline the trainings, CTB created a set of generic training modules for the introduction of ND&R, as well as "Job Aids", treatment algorithms and technical guidance documents.[11] A "quality improvement tool" was also developed to ensure a good quality of patient care would be implemented at all treatment sites.

Staff working on monitoring and evaluation also benefited from technical support, receiving trainings on cohort analyses, including via webinars.

STRENGTHENING OF LABORATORY NETWORK

CTB provided technical assistance for the expansion of the diagnostic network, including support for the increase of laboratories able to perform Xpert MTB/RIF, as well as second-line line probe assay (SL-LPA) and phenotypic DST (pDST). The introduction of rapid molecular tests allowed the reduction in time to diagnosis and treatment initiation from several months to just a few days. CTB also supported the doctors in designing the most appropriate treatment regimen by facilitating trainings on the clinical interpretation of test results.

ACTIVE TB DRUG-SAFETY MONITORING AND MANAGEMENT (aDSM)

aDSM is defined as the active and systematic clinical and laboratory assessment of patients on treatment with new TB medicines, novel MDR-TB regimens or XDR-TB regimens to detect, manage and report suspected or confirmed drug toxicities.[12] aDSM is a fundamental component of PMDT. CTB supported introduction of aDSM hand-in-hand with the introduction of ND&R. Trainings and technical assistance where provided on how to develop national aDSM guidelines and policies. CTB also provided the necessary resources for aDSM to be implemented, such as job aids, purchasing audiometers and electrocardiograms and trainings on how to use them, interpret their results and adjust treatment if needed. (Figure 3)

Countries also received guidance on the purchase of the appropriate equipment with tools developed under the project (see footnote). CTB also assisted the respective National Pharmacovigilance body in reporting severe adverse events to the GDF and the WHO Collaborating Centre for International Drug Monitoring, Uppsala, Sweden.

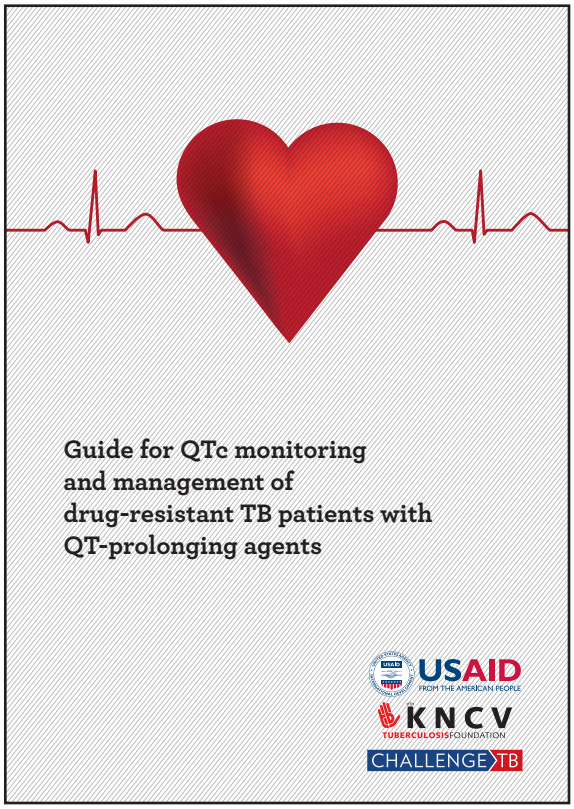


Figure 3. CTB Guide for monitoring and management of drug-resistant TB patients with QT-prolonging agents. Updated version, 2018[11]

MONITORING OF PROGRESS AND TARGETED STTA

CTB monitored monthly the speed of the progress of ND&R implementation. Monthly questionnaires and calls with CTB country offices were completed. Qualitative and quantitative data was collected, monthly country specific profiles developed and disseminated, and an overall progress dashboard was developed. This system identified gaps and helped to plan specific targeted STTA missions to tackle the focused issues identified via the monitoring mechanism. CTB also disseminated patient success stories for advocacy and education purposes, allowing readers to look through the data to see the real people beneath.

1. Guidance provided in Challenge TB Project 2017 documents "Requirements for QTc measurement in ECG monitoring when introducing new drugs and regimens for the treatment of DR-TB" and on "Audiometry in the management of DR-TB". Accessible via http://www.challengetb.org/library/pmdt

LESSONS LEARNED

NEED FOR AN ADVOCACY PLAN

Prior to the introduction of ND&R, there was an unexpectedly high need for advocacy at the country level. Regulatory and professional associations in some countries considered that there was insufficient evidence for the use of ND&R because Bdq, Dlm, and the STR had all been given "conditional" recommendations by WHO. Additionally, Bdq had only conditional approvals by the FDA and the EMA, and Dlm from the EMA.

When dealing with regulatory authorities and the introduction of new interventions, an advocacy plan is needed beforehand to effectively address policy makers concerns. The presentation of information in technical working groups and visits to the pilot sites already implementing the activity helped to build confidence. The introduction of aDSM as a mean of monitoring and reporting the adverse events related to the drugs helped lessen worries about the safety of the drugs and regimens. Sharing the early results of the implementation motivated health professionals working in other sites and helped to accelerate the roll out of the ND&R in new sites within the respective country and across countries.

Advocacy is also needed to keep the introduction of ND&R high on the agenda in countries that have a low burden of DR-TB and/or have many other competing priorities.

NEED FOR A SOLID IMPLEMENTATION PLAN

Utilization of the implementation planning tool allowed countries to identify what existed in country, what was needed to introduce ND&R, and the varies resources available in the country that could be used to support the introduction of ND&R. The development of a solid implementation plan was important in order to lay out the various tasks and responsibilities of all stakeholders involved. Progress could be monitored against the agreed implementation plan. The process of introducing ND&R in countries was lengthy. Although timelines varied slightly from country to country, it took up to approximately two years to move from initial advocacy activities for the introduction of ND&R, to changing of policies and to the introduction of ND&R at pilot sites. However in Kyrgyzstan, once the initial pilots sites had been established, it took only 12 months to expand to nationwide coverage and access.

NEED FOR A MULTI-PRONGED APPROACH TO CREATE A ROBUST LABORATORY NETWORK

The implementation of ND&R, based on a triage approach, requires the use of Xpert MTB/RIF and SL-LPA for diagnosis and proper allocation of treatment. A robust laboratory network is needed to cater to the populations' needs across the respective countries and should not limit the use of ND&R to a few treatment sites only.

For the roll out of ND&R, a multi-pronged approach was needed with crucially expansion and strengthening of the laboratory networks. Sample transportation networks had to be reinforced and expanded to cater to new treatment sites. Training of laboratory staff in the new techniques and of health care practitioners in the use and interpretation of results, was also needed. Digital connectivity solutions software, aiming at decreasing the turnaround time of results, was also introduced.

NEED OF A QUALITY IMPROVEMENT PLAN

A quality improvement plan was needed in order to ensure that quality of patient care was maintained after the roll-out of ND&R. Besides initial theoretical trainings, clinicians continued receiving on the job training and supportive supervision. Job aids, algorithms

and technical documents were created and widely distributed.[11] National concilia continued receiving support to strengthen the knowledge of their members and a "Quality Improvement Tool" was adapted from earlier tools developed by other actors and upgraded for use by supervisors and specialists working for the respective National TB Programs (NTPs) and partner organizations.

TIMELY DRUG FORECASTING AND PROCUREMENT

Despite a successful implementation, roll out of ND&R to more treatment sites was hampered in some countries due to a lack of an adequate number of drugs to treat all the patients in need. Due to the long lead times, there is a need to initiate the estimation of the number of patients needing each regimen as early as possible. Regulatory issues for the importation of the drugs into the country have to be tackled early on and plans have to be in place in case a transition of drug procurement mechanism is needed. An example would be the transition from Global Fund support to national funding for drug procurement. In fact, the whole drug supply system was affected and required strengthening and/or addressing the challenges faced. The CTB project provided technical assistance to support countries resolve the varied issues.

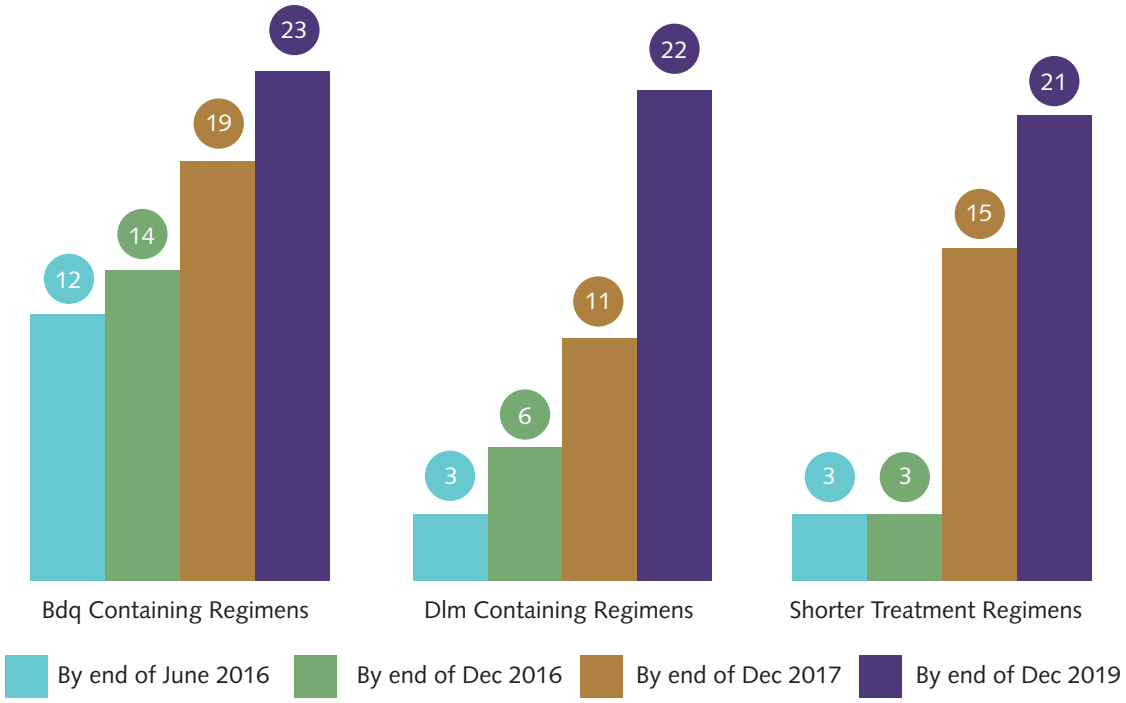
OFF LABEL USE OF BDQ AND DLM

With the increased accessibility of the ND&R and a greater use of both new drugs, more DR-TB cases were found who to needed the use of the drugs in an "off-label" manner. Patients that presented with extensive patterns of drug resistance and hence who had limited treatment options, either needed the use of both Bdq and Dlm for an extended period of time (i.e. greater than the currently recommended 6 months) and/or their use in combination. Pregnant women, children and patients with extra- pulmonary TB also required off label use of the drugs. Regulatory authorities in some countries were reluctant to allow the off label use of the drugs until in 2017, WHO released a best-practice statement on the off-label use of Bdq and Dlm for the treatment of MDR-TB.[13] In the future when new drugs or treatment regimens are to be introduced, it would be advisable to already have guidance on the off label use and a common understanding with the relevant stakeholders.

RESULTS

As of early October 2018, all 23 CTB countries had introduced an individualized treatment regimen containing Bdq (ITR-Bdq). By the end of June 2019, twenty-one have introduced the STR, and 22 countries an ITR containing Delamanid (ITR-Dlm, often in combination with Bdq - ITR-Bdq+Dlm) (Figure 4). The last remaining countries are in the process of ordering drugs for the introduction of the STR and ITR-Dlm, and most likely will introduce said drugs and regimens in the second half of 2019.

Figure 4. Countries introducing ND&R, June 2016 – June 2019 (n=23)



Between June 2016 and June 2019, cumulatively 9,407 patients had been enrolled on an ITR-Bdq, 673 on an ITR-Dlm, 418 on an ITR-Bdq+Dlm, and 16,118 had been enrolled on the STR across the countries supported by CTB (Table 1). Although India introduced the STR in 2018, there is no available data on the number of patients enrolled. By the end of December 2018, the number of treatment sites for Bdq or Dlm had increased to 385 from 33 at the end of 2016.

Table 1. Summary of patient enrollment 2016 – 2019

	ITR-Bdq	ITR-Dlm	STR	ITR-Bdq+Dlm
National number of patients reported as enrolled from Jan to Dec 2016 (# of countries that reported data to CTB)	556 (11 countries)	30 (5 countries)	972 (5 countries)	9 (2 countries)
National number of patients reported as enrolled from Jan to Dec 2017	1,636 (18 countries)	244 (10 countries)	2,380 (16 countries)	36 (4 countries)
National number of patients reported as enrolled from Jan to Dec 2018	4,743 (22 countries)	221 (16 countries)	8,363 (20 countries)	180 (11 countries)
National number of patients reported as enrolled from Jan to June 2019	2,463 (20 countries)	178 (16 countries)	4,403 (18 countries)	193 (9 countries)

TREATMENT OUTCOMES

Interim treatment outcomes from patients treated with a Bdq-containing regimen show promising results, with 71% having a negative culture at the end of six months of treatment (Table 2). Final treatment outcomes for the 2016 cohort of patients show a success rate of around 60% (Table 3). Considering that at the beginning of the introduction of Bdq, most patients that qualified for treatment with Bdq at a country level were patients with either extensive patterns of resistance including XDR-TB and/or advanced disease with a global success rate of less than 35%, the reported achievements should be seen as a major success.

Table 2. ITR-Bdq interim treatment outcome results (at end of 6 months of treatment) for DR-TB patients enrolled on treatment from January 2017 to June 2018

Country	Year	Number of patients enrolled on treatment[1]	Interim treatment outcomes					
			Culture negative at 6 months[2]		Died by 6 months		Lost to Follow-Up by 6 months	
			#	%	#	%	#	%
Afghanistan	2017	2	2	100%	0	0%	0	0%
Burma/Myanmar		11	9	82%	1	9%	0	0%
Cambodia		2	2	100%	0	0%	0	0%
DRC		23	19	83%	4	17%	0	0%
Ethiopia (ALERT Hospital only)		9	8	88.9%	1	11.1%	0	0%
Indonesia		163	70	43%	20	12%	35	22%
Kyrgyzstan		60	53	88%	3	5%	6	10%
Mozambique (CTB supported areas [SA])		1	1	100%	0	0%	0	0%
Nigeria (12 CTB supported states [SS])		3	3	100%	0	0%	0	0%
Tajikistan		46	40	87%	3	6.5%	1	2.2%
Ukraine		46	42	91%	0	0%	3	7%
Total		**366**	**249**	**68%**	**32**	**8.7%**	**45**	**12.3%**
Afghanistan	2018 (Jan to June)	6	4	66.6%	1	16.7%	1	16.7%
Burma/Myanmar		45	34	76%	9	20%	2	4%
Cambodia		8	6	75%	2	25%	0	0%
DRC		6	5	83%	1	17%	0	0%
Ethiopia (ALERT Hospital only)		4	4	100%	0	0%	0	0%
Indonesia		100	43	43%	13	13%	8	8%
Kazakhstan CTB		75	67	89%	3	4%	2	2.7%
Mozambique (CTB SA)		3	2	67%	0	0%	0	0%
Nigeria (12 CTB SS)		22	10	45%	9	41%	0	0%
Tajikistan		63	54	85.7%	3	4.8%	0	0%
Ukraine		81	78	96%	2	2%	0	0%
Total		**413**	**307**	**74.3%**	**43**	**10.4%**	**13**	**3.1%**
Combined totals		**779**	**556**	**71.4%**	**75**	**9.6%**	**58**	**7.4%**

1. Only laboratory confirmed RR-TB, MDR-TB, pre-extensively drug-resistant TB and extensively drug-resistant TB (XDR-TB) cases who have started treatment are to be counted for the reporting of Interim treatment outcome results. When calculating the proportion of cases with negative culture by 6 months, all patients started on treatment remain in the denominator, including patients who have died or were lost to follow-up before the end of 6 months of treatment. If a patient is lost to follow up and then dies before the end of the 6th month of treatment, then the result retained will be "Lost to follow-up", having been the first outcome reported.
2. Based on result of last culture performed and available after the patient has completed 6 month of treatment

Table 3. ITR-Bdq final treatment outcome results for DR-TB patients enrolled from 1 January to 30 December 2016

Country	Year	Number of patients enrolled on treatment during the cohort reporting period	Final Treatment Outcomes												Still on treatment	
			Cured		Treatment Completed		Treatment failed		Died		Lost to Follow-Up		Not evaluated			
			#	%	#	%	#	%	#	%	#	%	#	%	#	%
Burma	2016	12	5	42	2	17	0	0	4	33	1	8	0	0	0	0
DRC		18	0	0	7	39	0	0	11	61	0	0	0	0	0	0
Indonesia		43	25	58	3	7	8	19	4	9	3	7	0	0	0	0
Tajikistan		12	8	66.7	0	0	2	16.7	1	8.3	0	0	0	0	1	8.3
Total		**85**	**38**	**44.7%**	**12**	**14.1%**	**10**	**11.8%**	**20**	**23.5%**	**4**	**4.7%**	**0**	**0%**	**1**	**1.2%**

Successful final treatment outcomes for patients on ITR with Dlm were high, with 87.5% being cured. Although the number of patients in the cohorts were small, the initial results are very promising (Table 4).

Table 4. ITR-Dlm final treatment outcome results for DR-TB patients enrolled from 1 January 2016 to 30 June 2017

Country	Year	Number of patients enrolled on treatment during the cohort reporting period	Final Treatment Outcomes												Still on treatment	
			Cured		Treatment Completed		Treatment failed		Died		Lost to Follow-Up		Not evaluated			
			#	%	#	%	#	%	#	%	#	%	#	%	#	%
Burma	2016	7	6	86	0	0	0	0	1	14	0	0	0	0	0	0
Total		7	6	86	0	0	0	0	1	14	0	0	0	0	0	0
Namibia	2017 Jan to June	1	1	100	0	0	0	0	0	0	0	0	0	0	0	0
Total		**1**	**1**	**100**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**
Combined Total		**8**	**7**	**87.5%**	**0**	**0%**	**0**	**0%**	**1**	**12.5%**	**0**	**0%**	**0**	**0%**	**0**	**0%**

High treatment success rates (range 67-89%, mean 77.4%) were reported from seven countries (Burma, Cambodia, DRC, Kyrgyzstan, Namibia, Tajikistan, and Zambia) on 1,084 patients enrolled on the STR in 2017. This is a significant improvement on the globally reported success rate of 55% for MDR-TB patients.[1] However, the results observed in Indonesia have not been as good, with only 51% success. A very high lost to follow-up rate of 24.3% and a death rate of 14.3% were reported, the causes of which need urgent further analysis whilst solutions are found to bring these rates down.

The introduction of aDSM has gone hand-in-hand with the introduction of ND&R in CTB-supported countries. An increasing number of countries, where ND&R have been introduced with CTB support, are reporting serious adverse events (SAEs), which implies that countries are implementing aDSM systems. There has been a steady increase in the number of countries reporting SAEs under aDSM systems. In 2016, 105 SAE were reported in patients being treated with ITR-Bdq from 5 countries. By the end of 2018, 536 SAEs were reported from 18 countries.

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CONCLUSIONS

ND&R have been successfully implemented under programmatic conditions in all CTB supported countries. Although it took up to two years to move from the initial advocacy activities promoting the introduction of ND&R to initiation of the first cohort of patients on treatment, further expansion was rapid. The number of sites with access to ND&R has sharply risen in only two years, and the number of patients benefiting from these treatments has accordingly increased significantly. ND&R can be implemented in different settings with good outcomes if a stepwise approach is taken, and efforts are coordinated with all other actors. The lessons learned from this intervention can be replicated for the introduction of newer treatment regimens which are expected in the not so distant future.

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