



GLOBAL DR-TB INITIATIVE TRIAGE TASK FORCE

Report of the GDI Triage Task Force

June 2017

In May 2016, WHO recommended the programmatic use of the nine-month treatment regimen for multidrug-resistant TB (MDR-TB) consisting of an intensive phase of 4 (-6) months Km-Mfx-Pto-Cfz-Z-H_{high-dose}-E followed by a continuation phase of 5 months of Mfx-Cfz-Z-E for patients with no resistance or suspected ineffectiveness to any medicine in the regimen (except isoniazid), no exposure to more than one second-line drug (SLD) in the regimen for more than one month, no intolerance to more than one medicine in the regimen or risk of toxicity, not pregnant and have no extrapulmonary TB disease. Also at this time, WHO recommended to use second-line (SL) LPA in patients with confirmed rifampicin-resistant (RR) TB or MDR-TB as the initial test to detect resistance to fluoroquinolones (FQ) and the SL injectables (SLI), instead of the phenotypic culture-based drug susceptibility testing (DST). These were milestone recommendations as they opened the possibility of rapid triage of RR-/MDR-TB patients to treatment with either a shorter regimen or longer (20-24 months) regimen with new and repurposed drugs. This triage approach significantly reduces the diagnostic delay as well as the duration of treatment for many patients while improving treatment success rates due to earlier treatment start.

A number of countries are known to be implementing the shorter treatment regimen (STR) and/or have access to SL-LPA; however, there is limited information about the status of their programmatic use and the numbers of patients reached. The GDI Triage Task Force (Triage TF), coordinated by the KNCV Tuberculosis Foundation, The Hague, The Netherlands, was created in November 2016 to address this information gap. The Triage TF is mandated to monitor and support the implementation of the STR and SL-LPA in the context of the patient triage approach by collecting data in collaboration with other technical agencies on their introduction to countries, patient enrolment on STR, expansion, lessons learned, challenges and technical assistance (TA) needs. This information intends to feed into drug and test production and forecasts, identify country TA needs, and contribute to the global body of evidence as data are being shared with the global support mechanisms dealing with policy guidance, technical assistance, procurement and supply chain management.

Results of data collection on the STR and the SL-LPA

the Triage TF has collaborated with the following technical agencies since November 2016, and has gathered information from at least 64 countries that are implementing the STR, and/or the SL-LPA.

- The **GDI DR-TB STAT Task Force** (DR-STAT) in 2015 created a platform of collecting information through monthly emails to 36 countries on the cumulative number of patients enrolled on the new drugs, bedaquiline (Bdq), and delamanid (Dlm). The Triage TF requested DR-STAT to include

in its existing data gathering mechanism information on the use of SL-LPA, and the start date in countries. In March 2017, it also started collecting STR cumulative enrolment numbers.

- **The UNION** has been supporting the Francophone African countries in the implementation of the STR since 2013, and provided data to the Triage TF from 12 countries on the status of the STR and SL-LPA, and the challenges encountered by these countries as of February 2017.
- **Challenge TB (CTB) funded by USAID** supports 22 countries in Africa, Europe, Central Asia, and Asia in the introduction and implementation of new drugs and the STR through the patient triage approach, and shared data with the Triage TF on the quarterly STR enrolment number. More updated STR enrolment numbers and SL-LPA status were obtained through a one-time data collection in May 2017 including lessons learned, challenges and TA needs pertaining to their introduction and use.
- **The Global Drug Facility (GDF)** has information on TB drug orders; however, the drugs for STR are not specified at the central level. The Triage TF suggested to obtain data from the GDF regional focal persons who collect more detailed information during country missions on the 26 GDF priority countries. GDF plans to put in place an improved data collection mechanism to obtain information on STR drugs orders at the central level.
- **The regional Green Light Committees (rGLCs)** are involved in their respective countries' development of Global Fund Funding Requests (GF-FR) for 2018-2020 submitted in March and May 2017. The Triage TF reached out to the rGLCs to obtain information on the plans for STR and SL-LPA procurement; however, GF-FR proposals did not contain the exact information requested. During the GDI Core Group meeting on 9 June 2017, the rGLC Chairs presented information on the current status of the STR and new drugs implementation in their countries, some data in this report.
- **WHO** sent a comprehensive country questionnaire in the first quarter of 2017 to national TB programmes (NTPs) through the WHO regional offices for information on the introduction and scale up of the STR, the longer (20-month) MDR-TB treatment regimen, Bdq-containing, and Dlm-containing regimens. Included in the questionnaire are the a) status of STR implementation b) yearly patient enrolment numbers (adults and children) on the STR from 2013-2016, and 2017-2020; c) status of updated new drugs and regimen (ND&R) guidelines/ implementation plans; d) STR drug supply/order status; e) drug regulatory status; f) status of active TB drug-safety monitoring and management (aDSM) activities; g) status of diagnostic tools; h) available funding for STR drugs and aDSM; i) technical support needs; j) social support; and k) critical issues for ND&R implementation. Results of this extensive WHO questionnaire will be available in August 2017, the earliest. This report by the Triage TF serves as interim information on the STR and SL-LPA status in 64 countries one year after WHO recommendations on their use were issued.

Countries implementing the STR and SL-LPA

The lists of countries implementing the STR, SL-LPA, or both are limited to countries covered by the data collection undertaken by the Triage TF, DR-TB STAT, CTB, The UNION and the rGLCs.

Countries implementing the STR

At the time of the WHO recommendation in May 2016, there were 18 countries implementing the STR, including four involved in clinical trials (**Table 1, Figure 1**). As of June 2017, at least 39 countries were known to be implementing the STR, with 9 more countries in the procurement process of STR drugs targeting implementation within the year. By end 2017, there will be 48 countries using STR (**Table 1, Figure 2**), either as a pilot or under programmatic conditions.

Table 1. Countries implementing the STR

As of May 2016 18 countries	As of June 2017 39 countries	By end 2017 48 countries
Bangladesh, Benin, Burkina Faso, Burundi, Cameroon, Central African Republic, Cote d'Ivoire, DR Congo, Guinea, Niger, Rwanda, Senegal, Swaziland, Uzbekistan, Vietnam Under clinical trial: Ethiopia, Mongolia, South Africa (Vietnam)	Countries in the adjacent left except Ethiopia Plus Afghanistan, Chad, Djibouti, Egypt, Equatorial Guinea, Gabon, India, Iran, Kyrgyzstan, Laos PDR, Lesotho, Mali, Mauritania, Morocco, Mozambique, Pakistan, Papua New Guinea, Philippines, Sierra Leone, Somalia, South Sudan, Tajikistan	Countries in the adjacent left Plus Cambodia, Ethiopia, Indonesia, Madagascar, Myanmar, Nigeria, Tanzania, Zambia, Zimbabwe

Countries with capacity for SL-LPA

As of mid-May 2017, at least 36 countries were known to have capacity to perform SL-LPA, with 7 more countries in the procurement process of SL-LPA kits targeting use of the test within the year. By end 2017, there will be 43 countries using SL-LPA (**Table 2, and Figure 3**), either as part of a national algorithm or as an ad hoc test for SL resistance.

Table 2. Countries with capacity for SL-LPA

As of mid-May 2017 36 countries	By end 2017 43 countries
Armenia, Bangladesh, Belarus, Botswana, Cambodia, Cameroon, China, Cote d'Ivoire, DPR Korea, Estonia, Ethiopia, Georgia, Haiti, India, Kazakhstan, Kyrgyzstan, Laos PDR, Latvia, Madagascar, Myanmar, Mozambique, Namibia, Niger, Nigeria, Peru, Philippines, Russia, South Africa, Swaziland, Tajikistan, Thailand, Ukraine, Uzbekistan, Vietnam, Zambia, Zimbabwe	Countries on the left column Plus Benin, Burkina Faso, DR Congo, Guinea, Indonesia, Mali, Tanzania

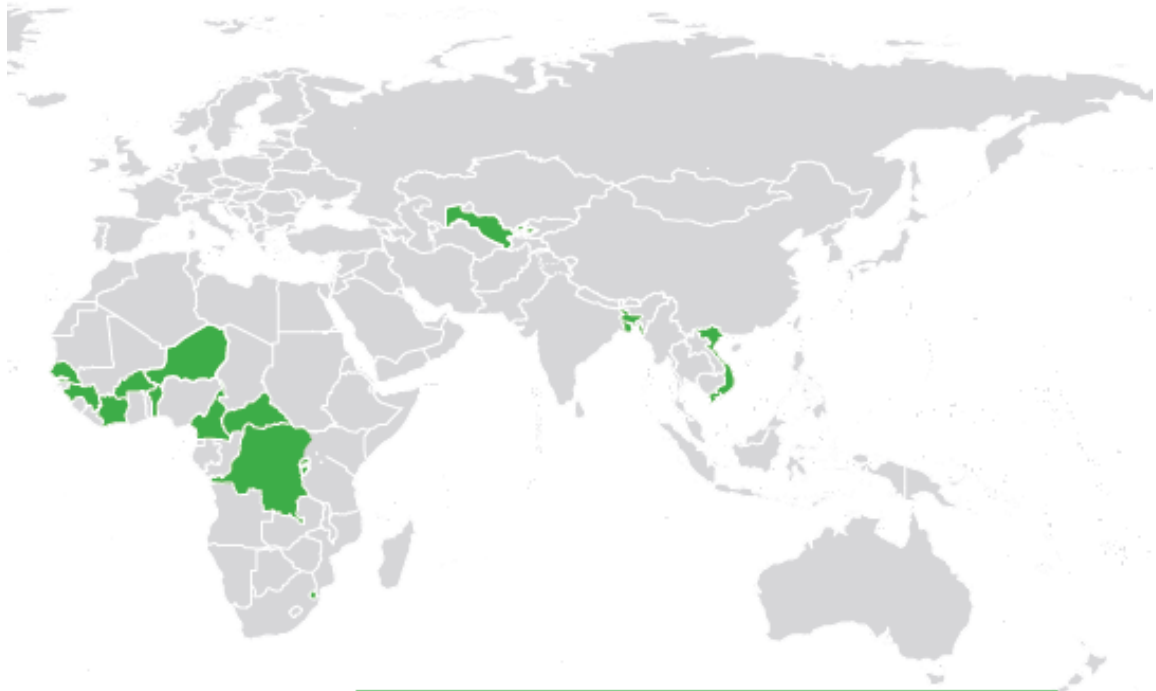
Countries implementing both the STR and the SL-LPA

As SL-LPA rapidly detects resistance to the FQ and/or SLI, it is an important eligibility test for the STR. In its absence, countries utilize clinical assessment for possible resistance, e.g., previous exposure through past use of the FQ and/or SLI or contact with a patient resistant to any of those drugs. The limitation of clinical assessment is, however, recognized. Patients started on the STR who turn out to be bacteriologically resistant to either the FQ and/or the SLI will have to be shifted to the longer regimen where key drugs such as moxifloxacin, kanamycin and clofazimine would have been compromised by their use in the STR. The Triage TF gathered that as of June 2017, among 61 countries that have at least the STR or SL-LPA in-country, only 14 (23%) are implementing both (**Table 3, Figure 4**), with another 14 in the procurement process of drugs and/or kits. By end 2017, there will be 28 (44%) out of 64 countries implementing both the STR and SL-LPA, either as a pilot or under programmatic conditions.

Table 3. Countries implementing both the STR and the SL-LPA

As of June 2017 14 countries	By end 2017 28 countries
Bangladesh, Cameroon, Cote d'Ivoire, Kyrgyzstan, India, Laos PDR, Mozambique, Niger, Philippines, South Africa, Swaziland, Tajikistan, Uzbekistan, Vietnam	Countries on the left column Plus Benin, Burkina Faso, Cambodia, DR Congo, Ethiopia, Guinea Conakry, Indonesia, Madagascar, Mali, Myanmar, Nigeria, Tanzania, Zambia, Zimbabwe

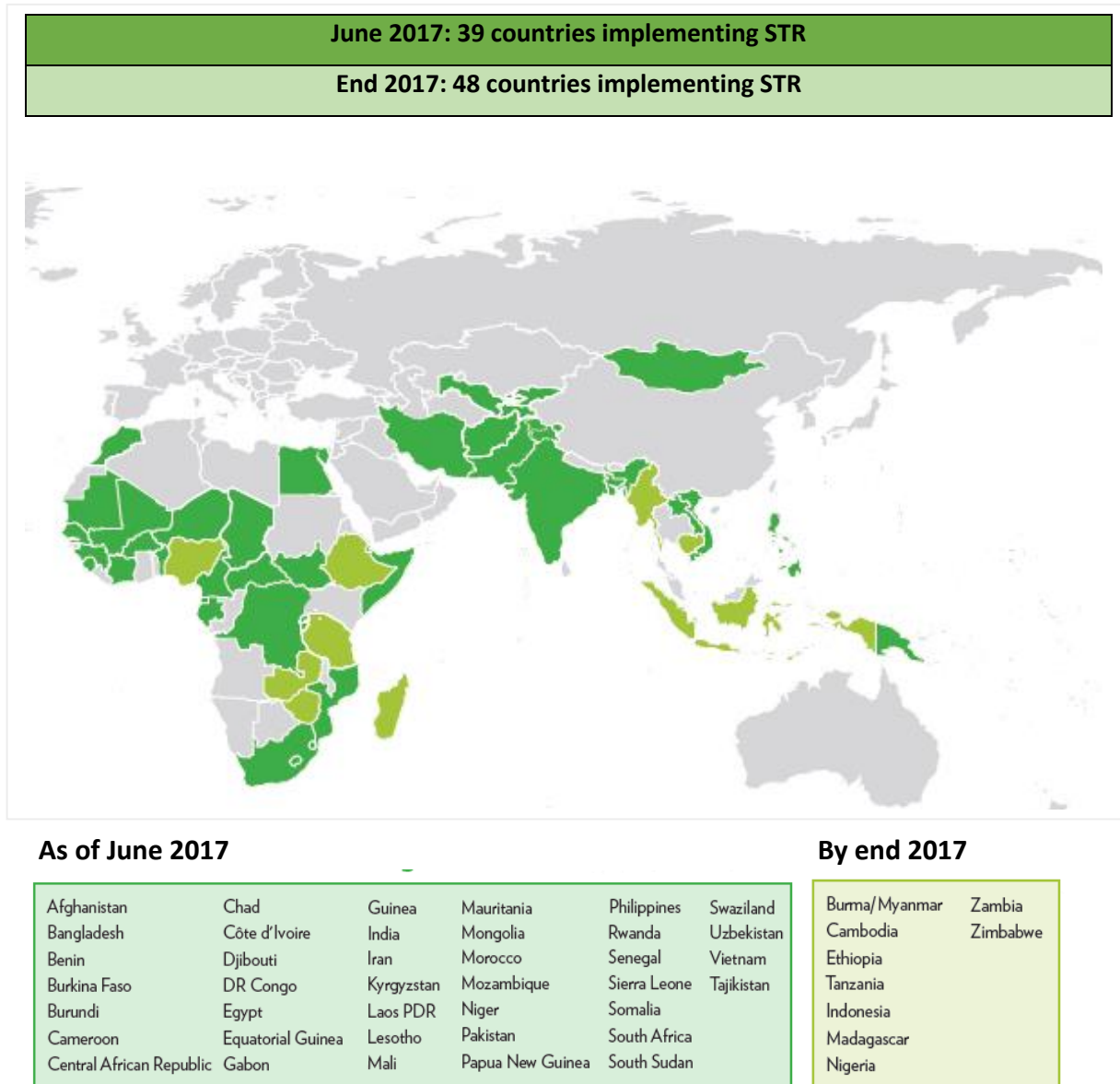
Figure 1. Countries implementing the STR, May 2016



Bangladesh	Central African Republic	Rwanda
Benin	Côte d'Ivoire	Senegal
Burkina Faso	DR Congo	Swaziland
Burundi	Guinea	Uzbekistan
Cameroon	Niger	Vietnam

In clinical trials: Ethiopia, Mongolia, South Africa, (Vietnam)

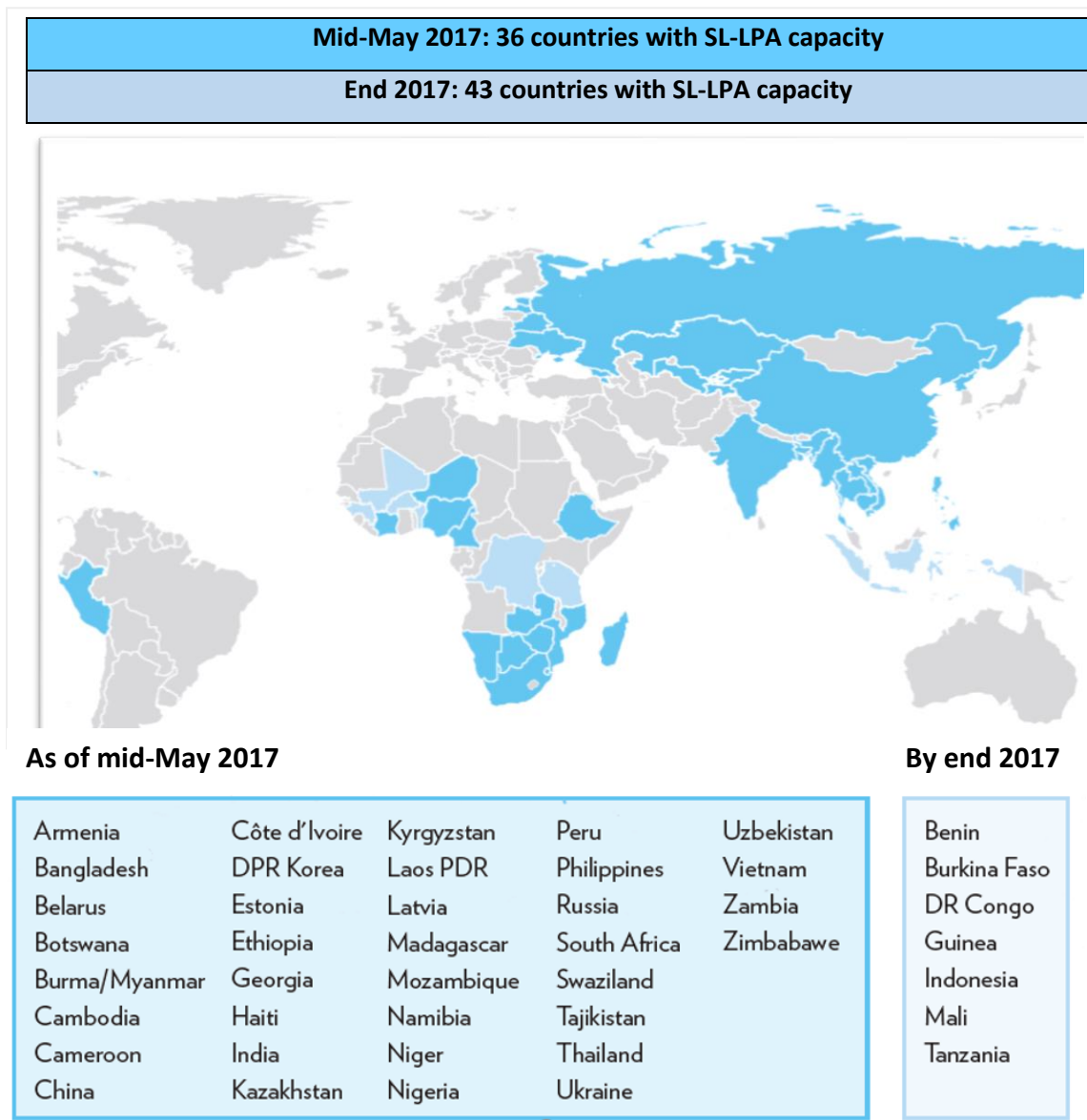
Figure 2. Countries implementing the STR, as of June 2017 and by end 2017



Gathered by GDI Triage TF from data sources: GDI DR-TB STAT TF, CTB, The UNION and rGLCs

Note: The countries in grey either a) had not yet started STR implementation as of the cut-off dates of reporting; or b) were not among the countries where STR data were collected by the GDI Triage Task Force and other technical agencies; or c) were unable to respond to the questionnaire for one reason or another. A more comprehensive data collection on STR implementation covering all countries is now underway led by WHO.

Figure 3. Countries with SL-LPA capacity, as of mid-May 2017 and by end 2017

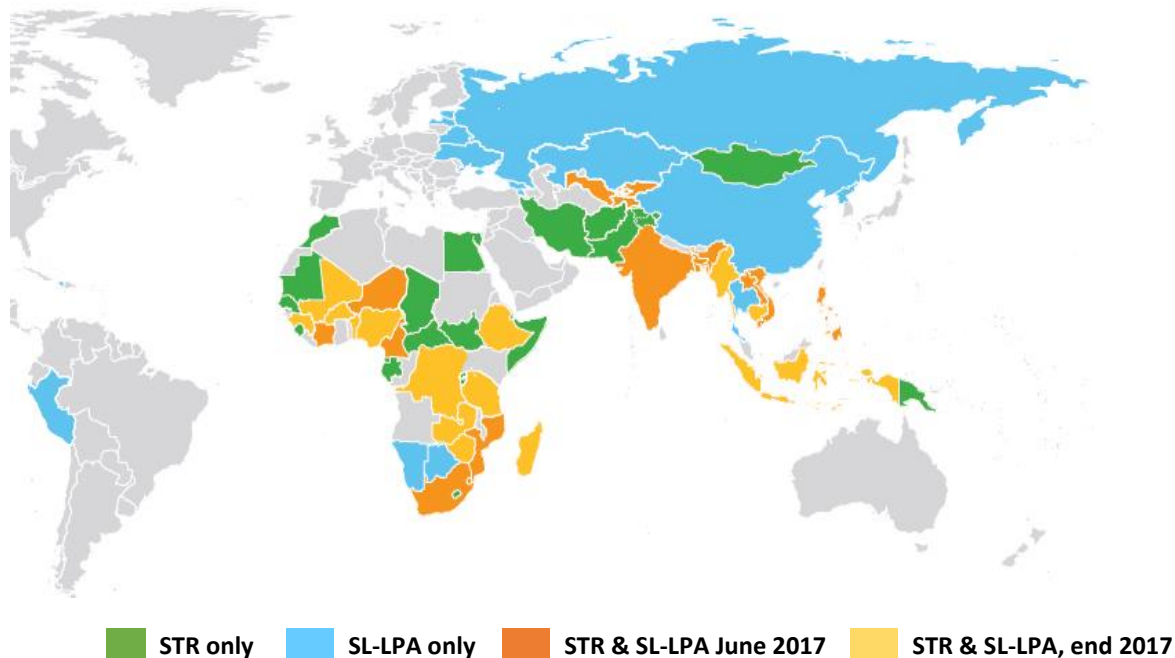


Gathered by GDI Triage TF from data sources: GDI DR-TB STAT TF, CTB, The UNION and rGLCs

Note: The countries in grey either a) did not yet have capacity for SL-LPA as of the cut-off dates of reporting; or b) were not among the countries where SL-LPA data were collected by the GDI Triage Task Force and other technical agencies; or c) were unable to respond to the questionnaire for one reason or another. A more comprehensive data collection on SL-LPA implementation covering all countries is now underway led by WHO.

Figure 4. Countries implementing the STR and with SL-LPA capacity, as of June and by end 2017

June 2017: 14 countries implementing the STR and with SL-LPA capacity
End 2017: 28 countries implementing the STR and with SL-LPA capacity



As of June 2017

Bangladesh	Laos PDR	Swaziland
Cameroon	Mozambique	Tajikistan
Cote d'Ivoire	Niger	Uzbekistan
Kyrgyzstan	Philippines	Vietnam
India	South Africa	

By end 2017

Benin	Ethiopia	Nigeria
Burkina Faso	Guinea Conakry	Tanzania
Burma/Myanmar	Indonesia	Zambia
Cambodia	Madagascar	Zimbabwe
DR Congo	Mali	

Gathered by GDI Triage TF from data sources: GDI DR-TB STAT TF, CTB, The UNION and rGLCs

Note: The countries in grey either a) had not yet started STR and/or SL-LPA implementation as of the cut-off dates of reporting; or b) were not among the countries where STR and SL-LPA data were collected by the GDI Triage Task Force and other technical agencies; or c) were unable to respond to the questionnaire for one reason or another. A more comprehensive data collection covering all countries is now underway led by WHO.

Number of patients enrolled on the STR

A few technical partners collect data on STR enrolment numbers in countries. Four different data collection periods were noted in the recent months from various sources.

- By end December 2016: 549 patients were cumulatively started on STR in 3 of the 22 CTB countries (*Source: CTB Annual Report, 2016*)
- By March 2017: 825 patients in 7 CTB countries (*Source: CTB Quarterly Report, Jan-Mar 2017*)
- By April 2017: 2,609 patients in 10 countries reported by DR-TB STAT (3 overlapping with CTB) (*Source: drtb-stat.org/country updates*)

By June 2017, in collaboration with partners, the Triage TF gathered a cumulative number of 4,985 patients in 19 out of 39 countries known to be implementing the STR since 2015, as shown in Figure 2 (**Table 4**). The data sources are the DR-STAT update in April 2017, CTB through a one-time data collection in May 2017, rGLC reports during the GDI Core Group meeting in June 2017, and personal communication in May 2017. These numbers are a combination of enrolments under pilot, observational studies and program conditions. These data are limited to countries covered by the Triage TF and other technical agencies, and are not all-inclusive. The fact that only DR Congo and Niger had numbers (available through DR-STAT) among the 15 Union-supported Francophone African countries underscores the limited information available on STR enrolment numbers. A comprehensive data collection is underway led by WHO in collaboration with rGLCs and the regional WHO offices.

Table 4. Countries with available STR enrolment numbers, from different data sources ^{a, b, c, d}

^a DR-STAT as of Apr 2017 ^b CTB as of 15 May 2017 ^c rGLCs as of June 2017

^d Personal communication as of May 2017

Country	No. of patients	Country	No. of patients
1. Afghanistan	130 ^c	11. Pakistan	60 ^c
2. Bangladesh	1775 ^{a, b}	12. Papua New Guinea	11 ^a
3. Djibouti	2 ^c	13. Philippines	503 ^d
4. DR Congo	578 ^b	14. Somalia	200 ^c
5. Egypt	244 ^c	15. South Africa	250 ^a
6. Iran	200 ^c	16. Swaziland	140 ^a
7. Kyrgyzstan	58 ^b	17. Tajikistan	28 ^b
8. Morocco	230 ^c	18. Uzbekistan	146 ^a
9. Mozambique	70 ^b	19. Vietnam	104 ^b
10. Niger	256 ^a		
TOTAL: 4,985			

Status of the 30 high MDR-TB burden countries

Long turn-around time of results and length of MDR-TB treatment have been barriers to proper diagnosis and treatment, and the introduction of SL-LPA and STR are amongst the solutions. Based on available data, of the 30 high MDR-TB burden countries globally, 14 are known to be implementing both the STR and SL-LPA by end 2017; 4 currently have the STR, but with no plans of SL-LPA use by end of the year; and 8 currently have SL-LPA capacity, but with no plans of implementing the STR by the end of the year (**Table 5**). The STR and SL-LPA status in four countries in AFRO and EURO was not known to the Triage TF as of June 2017 based on available data from technical partners. It is worth noting that all 14 countries with both the STR and SL-LPA are also implementing the use of new drugs, Bdq and/or Dlm, thereby, able to apply the full triage approach among RR-/MDR-TB patients.

Table 5. Status of the STR and SL-LPA in the 30 high-MDR-TB burden countries by end 2017

WHO Region	Both STR & SL-LPA <i>(all countries are also implementing new drugs)</i>	STR only	SL-LPA only	Not known
AFRO	Ethiopia Mozambique Nigeria S. Africa Zimbabwe	DRC		Angola Kenya
EURO	Uzbekistan Kyrgyzstan Tajikistan		Kazakhstan Russia Ukraine Belarus	Azerbaijan Moldova
EMRO		Pakistan Somalia		
PAHO			Peru	
SEARO	Bangladesh India Indonesia Myanmar		DPRK Thailand	
WPRO	Philippines Vietnam	PNG	China	

Modifications to the WHO Regimen

Source: Triage TF one-time data collection, CTB countries

Some countries which started using the STR prior to the WHO recommendation in May 2016 are applying shorter regimens that are slightly different from the WHO recommended regimen or drug dosage. **Table 6** lists the modifications gathered from CTB countries in May 2017.

The UNION-supported countries also use normal rather than high-dose moxifloxacin (Mfx). There is no published study yet on the long-term use of high-dose Mfx at the moment.

Table 6. Modifications to the WHO regimen and dosage in certain settings

Modification to the WHO regimen (and/or dosage)	Country
High-dose Lfx instead of high-dose Mfx	Bangladesh (Damien Foundation-supported areas) Vietnam
Normal (400 mg) instead of high-dose Mfx	Bangladesh (NTP) Kyrgyzstan Tajikistan

Lessons learnt, challenges, and technical assistance needs in STR and SL-LPA implementation

Around 13 CTB countries responded to the questionnaire which included lessons learnt, challenges and TA needs in the implementation of the STR and SL-LPA in May 2017. The UNION shared challenges encountered by the 12 Francophone African countries in February 2017.

Lessons learnt and challenges

1. *WHO endorsements facilitated the implementation of the STR and SL-LPA.* WHO's recommendations for the programmatic use of the STR among eligible patients, and for SL-LPA to be the initial diagnostic test to detect SLD resistance among RR-/MDR-TB patients facilitated the implementation of these innovations, while recognizing the need for ample preparation. Countries with existing LPA capacity for first-line drugs noted strengthening of this capacity as WHO recommended its routine use for SLDs among RR-/MDR-TB patients. However, some countries still require a local validation process for SL-LPA, which could take a long time. Also, with poor sputum transportation systems and consequent long turn-around time for results, the advantage of the rapid test may be lost.
2. *Concern on transition costs from conventional MDR regimen contributed to delay in STR uptake.* In 2016, countries were concerned how to justify the non-utilization of some Global Fund-procured SLDs as they transition from the conventional to the STR regimen, contributing to the delay in STR uptake. This was addressed when the Global Fund expressed its support to rapid STR introduction, acknowledging the benefits for patients and health systems, and the overall

cost savings when using the STR and the triage approach. Countries only need to submit a letter to the Global Fund Portfolio Manager requesting support for the transition to STR with an accompanying quantification of the medicines that will not be utilized.

3. *Preparation for the implementation of the STR entailed time.* Among the areas needing preparation time for STR implementation were updating the PMDT guidelines, training and development of information materials, transition plans and budgets. Some countries had difficulties in estimating the number of patients who will benefit from the STR and the initial cost of the regimen change, flagging the need for technical assistance and capacity building in this area. In addition, consensus building in countries also took time, resulting in lengthy reviews of implementation protocols, owing to perceived adverse drug effects, e.g. cardiotoxicity, and the concern of drug resistance not only to SLDs, but also to first-line agents, pyrazinamide and ethambutol.
4. *STR and SL-LPA implementation requires human resource augmentation.* As in many countries, the switch to the STR coincided with PMDT scale-up and the introduction of aDSM, requiring augmentation of the existing PMDT workforce both in the program and laboratory sides, which, in some settings, are already limited. It was a challenge to define roles and responsibilities, and to provide capacity building for the new innovations.
5. *Interpretation of LPA findings is not always straightforward.* In some countries, clinicians and laboratory staff have difficulty interpreting the LPA findings of genetic mutations, which occasionally show discordance from clinical assessment and phenotypic DST.
6. *Limited patient access during the introduction phase needs accompanying support.* Countries express difficult access to the STR among eligible patients during the introduction and pilot phase being available in only 1-2 sites. The same is true for SL-LPA, and monitoring tests during STR treatment, e.g., electrolytes, thyroid-stimulating hormone, audiometry and ECG. This underscores the need for accompanying support, such as patient enablers, an efficient specimen collection and transport mechanism, and scaling up of laboratory tests to peripheral treatment centers.

Technical assistance needs

Source: Triage one-time data collection, CTB countries

Technical agencies are closely collaborating with countries addressing specific needs through targeted TA missions for country preparedness and quality implementation of the new drugs, the STR, and SL-LPA. The following TA needs for the STR and SL-LPA were expressed by countries:

1. Planning and preparation for implementation (updating PMDT guidelines incorporating the new drugs, the STR and SL-LPA, developing SOPs and training materials, coordinating with existing partners assisting other areas, including the private sector)
2. Engagement of all stakeholders to agree on a road map, and country scale up for the STR and SL-LPA
3. Laboratory capacity scale-up (for SL-LPA & SL-DST), and their integration into the national diagnostic algorithm

4. Training, and capacity building for both laboratory staff and clinicians, including the interpretation of test results
5. aDSM, including management of adverse drug reactions (ADRs) and drug interactions
6. Drug quantification and importation
7. Recording and reporting (updating R & R forms, electronic tools)
8. Monitoring and supervision of the implementation of the new innovations

Next steps for the Triage TF in support of the implementation of the STR and SL-LPA

The technical partners are engaged in discussions with the GDI Core Group, Global Fund, GDF, WHO and suppliers to facilitate smooth uptake of the STR and SL-LPA. A discussion is ongoing regarding the creation of a global database for monitoring and measuring the progress of the introduction and implementation of new and repurposed drugs, the STR and SL-LPA.

The Triage TF proposes to continue as the focal point for collecting and collating information related to the STR and SL-LPA from countries in collaboration with the rGLCs, WHO Regional Offices and other technical partners. Given that the WHO questionnaire is comprehensive in scope, the Triage Task Force will propose to continue its focus on the STR and SL-LPA through the following activities:

1. Formally collaborate with the rGLCs and/or WHO Regional Offices to collect on a regular basis the cumulative patient enrolment numbers on the STR, SL-LPA utilization, and information on barriers to access to relevant diagnostics and medicines, technical assistance needs, etc., and undertake problem-solving actions, engaging relevant partners, depending on the issues at-hand.
2. Hold regular online discussions and webinars as a venue to share country issues, questions and challenges in STR and SL-LPA implementation. For every webinar, 1-2 countries will be invited to present their experience on the introduction and scale up of the STR and SL-LPA. For advanced countries, treatment outcomes will be discussed with reference to outcome definitions used vis-à-vis the official definition that will be released by WHO in collaboration with technical partners.
3. As SL-LPA is an important rapid test that supports the patient triage approach, laboratory experts will also be invited to speak on the proper interpretation of mutations of FQs, and SLIs, their correlation with SL-DST tests, and with clinical assessment to guide clinicians and program implementers in dealing with test results. Experts from the Global Laboratory Initiative (GLI) will be consulted for issues that need further clarification.
4. Deploy the Triage TF page on the GDI website and manage a website that brings up issues regarding implementation of the STR and SL-LPA and systematically provides progress updates. Discussions during the webinars, and the information from consenting countries through the rGLCs and other partners will be posted on this website.