



GLOBAL DR-TB INITIATIVE TRIAGE TASK FORCE

2018 Country uptake of the Shorter Treatment Regimen and the SL-LPA

Background

In December 2011, the World Health Organization (WHO) recommended rapid drug susceptibility testing (DST) using Xpert MTB/RIF as the initial test for rifampicin resistance¹. In May 2016, WHO released its recommendation for the programmatic use of a standardized shorter treatment regimen (STR)² for eligible rifampicin-resistant/multidrug-resistant (RR-/MDR-) TB patients. This 2016 WHO-recommended treatment consisted of an intensive phase of 4 (-6) months of Km-Mfx-Pto-Cfz-Z-H_{high-dose}-E³ followed by a 5-month continuation phase of Mfx-Cfz-Z-E. Also in 2016, WHO recommended the use of the second-line (SL) line probe assay (LPA) among patients with confirmed RR-/MDR-TB as the initial test to detect resistance to fluoroquinolones (FQ) and the SL injectables (SLI), instead of the phenotypic culture-based DST. The routine use of Xpert and the introduction of both the STR and SL-LPA have been strategic in rapidly triaging RR-/MDR-TB patients to the most appropriate treatment based on the best available evidence at that time, using either an STR or a longer (20-24 months) regimen with new and repurposed agents.

The GDI Triage Task Force (Triage TF), coordinated by the KNCV Tuberculosis Foundation in The Hague was created in November 2016 with the mandate 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 the country uptake of these two advancements. This information was intended to feed into the production of medicines and forecasts, identify country technical assistance (TA) needs, and contribute to the global body of evidence for policy guidance, TA, procurement and supply chain management.

This report is an update of the Task Force's June 2017 report published at the GDI website.⁴

¹ World Health Organization. Guidelines for the programmatic management of drug-resistant TB: 2011 update. 2011.

² World Health Organization. The Shorter Treatment Regimen, May 2016
https://www.who.int/tb/Short_MDR_regimen_factsheet.pdf

³ Acronyms: Km (Kanamycin), Mfx (Moxifloxacin), Pto (Prothionamide), Cfz (Clofazimine), Z (Pyrazinamide), H (isoniazid), E (Ethambutol)

⁴ Report of the GDI Triage Task Force, June 2018. (<http://www.stoptb.org/wg/mdrtb/taskforces.asp?tf=2>)

Data sources on the country uptake of the STR and the SL-LPA

The 2017 Triage TF report on the country uptake of the STR and the SL-LPA derived data from various sources such as the DR-TB STAT country update as of April 2017, Challenge TB (CTB) project report as of May 2017, rGLC presentation during the 7th GDI Core Group Meeting in Geneva in June 2017, the MDR-TB Working Group of the Union, and personal communication. For the 2018 report, the TF collaborated with technical agencies and groups using their respective reports with varied cut-off dates, as indicated in the text below. Data were then consolidated to come up with the total STR enrolment numbers per country, and a mapping of countries that are implementing the STR and/or the SL-LPA. Using data from the DR-TB STAT website, a mapping was also made that includes the use of new drugs, Bedaquiline (Bdq) and Delamanid (Dlm).

- **KNCV Tuberculosis Foundation implementing the CTB project**, the USAID flagship TB project since 2015. The CTB project supports the programmatic introduction and roll-out of new MDR-TB drugs and regimens in 22 countries in Africa, Europe, Central Asia, and South Asia using the patient triage approach. The CTB project's Annual 2018 Report (January-December) was used for this Triage TF Report. <https://www.challengetb.org/>.
- **DR-TB STAT Task Force** (DR-TB STAT) in 2015 created a platform of collecting information through monthly emails to countries on the cumulative number of patients enrolled on Bdq and Dlm. In March 2017, it started collecting cumulative STR enrolment numbers. The latest DR-TB STAT cumulative country update as of November 2018 was used for this Triage TF report taken from <http://drtb-stat.org/country-updates/>.⁵
- **The regional Green Light Committees (rGLCs) of the Eastern Mediterranean region (EMR), the Southeast Asia region (SEAR) and the Western Pacific region (WPR)** covering 27 countries responded to a one-time questionnaire sent out by the Triage TF in October 2018 regarding the use of the STR and the SL-LPA. EMR and SEAR rGLCs provided data up to June 2018, while WPR provided data up to December 2017 which are used in this TF report.
- **WHO - Geneva** conducted a one-time survey on national TB programmes' (NTP) use of new drugs and regimens during the first quarter of 2017 through the WHO regional offices and garnered responses from all 6 WHO regions covering 66 of the 194 member states. Information included actual patient enrolment numbers on the STR (adults and children) per country from 2013-2016 and the SL-LPA uptake up to December 2016. It also gathered information on indicative STR enrolment numbers and plans for LPA introduction in 2017-2020; however, these were not considered in this Triage TF report, and only the actual STR enrollment numbers and the SL-LPA status as of 2016 were used.
- **2018 publication by A. Trebucq, et. al. in the International Journal of TB and lung disease** on the 9 African countries that enrolled patients on the STR between 1 January 2013 and 31 March 2015.⁶

⁵ DR-TB STAT Country Updates, December 2018 (Data include updates through November 2018)

⁶ Trebucq A, Schwoebel V, Rieder L, et. al. Treatment outcome with a short multidrug-resistant tuberculosis regimen in nine African countries. *Int J Tuberc Lung Dis* Jan 1 2018;22(1):17-25.

Country uptake of the STR and the SL-LPA

A. Number of patients enrolled on the STR

As of June 2017, the Triage TF reported at least 4,985 patients initiated on the STR from 19 countries. In that report, 20 other countries were known to have been implementing the STR but did not have enrolment numbers available. The current report shows a five-fold increase with at least 25,000 patients enrolled on the STR (**Figure 1**) as of December 2018. **Table 1** lists 70 countries that have implemented the STR as of this date, 62 of which contributed to the 25,000 enrolled patients, and the remaining 8 countries with no available enrolment data. Twelve of the 62 countries enrolled children <15 years of age (N=94) that comprised less than 1% of all enrolled on the STR.

The numbers presented here include actual numbers reported by the various data sources mentioned above, and intentionally excluded indicative numbers planned to be enrolled to avoid over-estimation. Hence, the enrolment numbers are under-estimates of the actual figures. Also, this report does not indicate whether the STR enrolment was a pilot implementation or part of a nationwide roll-out.

Figure 1. Number of adults and children enrolled on the shorter treatment regimen as of June 2017 and December 2018

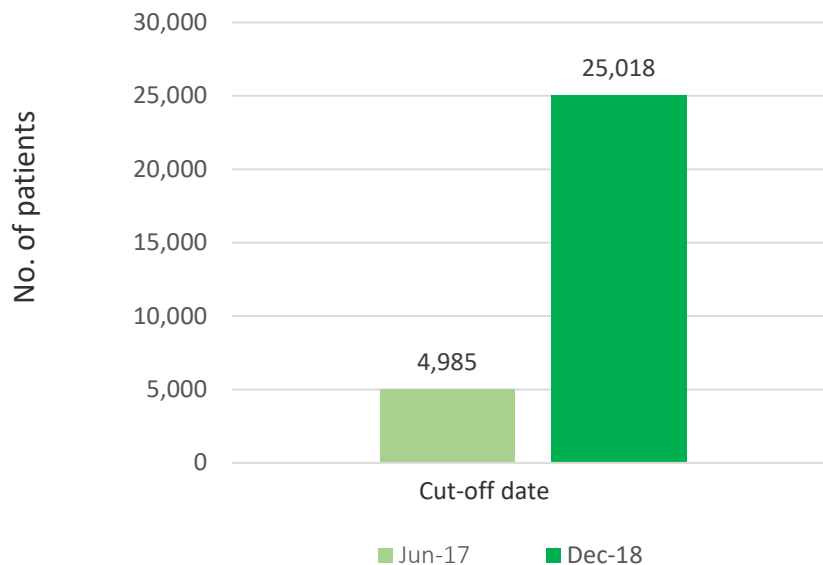


Table 1 lists the enrolment number per country and cites the data source(s) from which the number was derived. The data sources include the Triage TF Report of June 2017,⁴ the CTB Report of January-December 2018, the DR-TB STAT cumulative country update until November 2018,⁵ EMR, SEAR and WPR rGLC response to a TF questionnaire in October 2018, results of a WHO Survey (2013-2016), and a

2018 publication on the STR in the 9 African countries in the International Journal of Tuberculosis and Lung Disease.⁶ Countries with asterisks are those that included children.

Table 1. Number of adults and children enrolled on the STR per country as of December 2018

Data sources: ^a Triage TF Report June 2017⁽⁴⁾, ^b CTB Report January-December 2018, ^c DR-TB STAT country update cumulative till November 2018⁽⁵⁾, ^d rGLC response to TF Questionnaire October 2018, ^e WHO Survey 2013-2016, ^f 2018 publication in the Union⁽⁶⁾

Country	No. enrolled data source	Country	No. enrolled data source	Country	No. enrolled data source
1. Afghanistan	165 ^{a,d}	25. Guinea Equatorial	No data	49. Paraguay*	7 ^e
2. Australia	3 ^d	26. India	72 ^d	50. Philippines	6390 ^c
3. Bangladesh*	2252 ^{a,c}	27. Indonesia	2490 ^{b,d}	51. PITC**	10 ^d
4. Belarus	11 ^c	28. Iran	200 ^a	52. Rwanda*	202 ^e
5. Benin	29 ^f	29. Kazakhstan	119 ^b	53. Senegal	No data ^a
6. Bhutan	15 ^d	30. Kenya	165 ^c	54. Sierra Leone	No data ^a
7. Burkina Faso*	90 ^e	31. Kyrgyzstan	223 ^{a,b}	55. Singapore	4 ^d
8. Burma / Myanmar	328 ^{b,e}	32. Laos PDR	127 ^{d,e}	56. Somalia	223 ^{a,d}
9. Burundi*	186 ^e	33. Latvia	2 ^c	57. South Africa	3150 ^c
10. Cambodia	109 ^{b,e}	34. Lesotho	No data ^a	58. South Sudan	24 ^d
11. Cameroon*	432 ^e	35. Liberia	10 ^c	59. Sri Lanka	6 ^d
12. Central African Republic (RCA)*	45 ^f	37. Malawi	26 ^b	60. Swaziland*	242 ^c
13. Chad	100 ^e	37. Malaysia	20 ^d	61. Tajikistan	170 ^c
14. Costa Rica	7 ^e	38. Mali	No data ^a	62. Tanzania	209 ^b
15. Cote d'Ivoire	260 ^f	39. Mauritania	No data ^a	63. Thailand	116 ^d
16. Djibouti	75 ^d	40. Mongolia	56 ^{d,e}	64. Togo	28 ^e
17. DPR Korea	50 ^d	41. Morocco	230 ^a	65. Uganda	No data ^c
18. DR Congo*	1485 ^{a,b,e}	42. Mozambique	98 ^c	66. Ukraine	29 ^b
19. Egypt	244 ^a	43. Namibia	89 ^{b,c}	67. Uzbekistan*	399 ^{b,e}
20. Ethiopia	123 ^c	44. Nepal	75 ^d	68. Vietnam	1095 ^{a,b}
21. Gabon	11 ^e	45. Niger	376 ^c	69. Zambia	334 ^b
22. Georgia	10 ^c	46. Nigeria	1327 ^b	70. Zimbabwe	123 ^c
23. Ghana	No data ^d	47. Pakistan	410 ^{a,d}		
24. Guinea Conakry*	30 ^e	48. Papua New Guinea	72 ^{d,e}	TOTAL	25,018

* Enrolment included children <15 years old.

** Pacific Islands territories and countries (PITC) under WPR are considered as one representation in this report

B. Countries implementing the STR

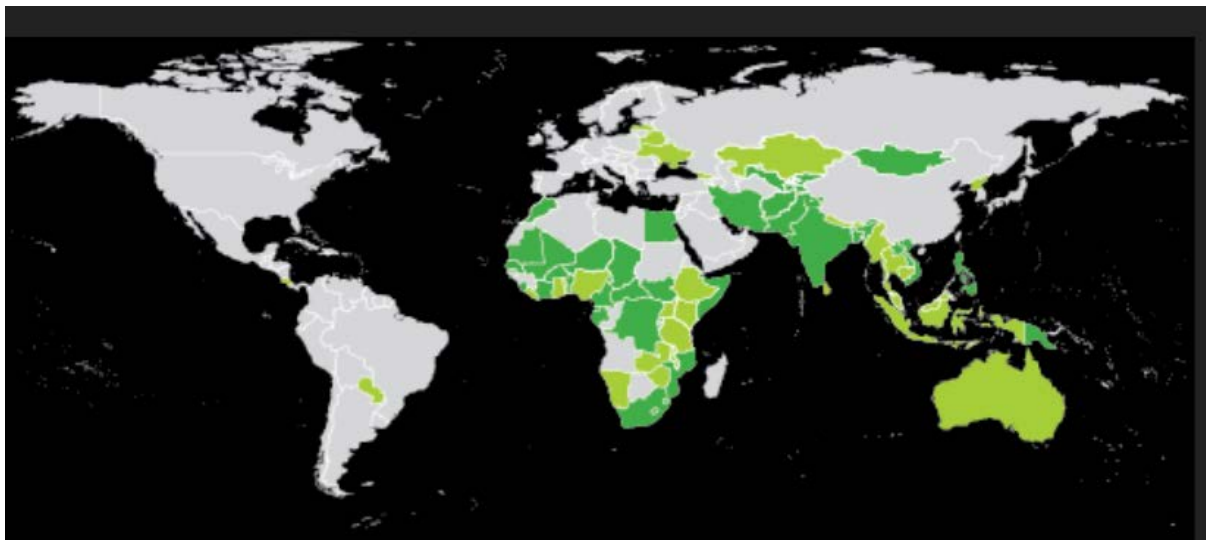
In the WHO recommendation for the use of the STR in May 2016, 18 countries were reported to be implementing the regimen, including 4 which participated in the STREAM STR clinical trial, namely, Ethiopia, Mongolia, South Africa and Vietnam.⁷ The 2017 Triage TF reported at least 39 countries that had introduced the STR as of June 2017 (**Table 2**),⁴ which has increased to 70 countries as of December 2018, almost 4X more than in 2016. **Figure 2** shows a mapping of these 70 countries.

⁷ The Union, STREAM clinical trial results provide vital insight into nine-month treatment regimen for multidrug-resistant tuberculosis (abstract). In: 48th Union World Conference on Lung Health; 11-14 October 2017; Guadalajara, Mexico

Table 2. Countries implementing the STR, 2016-2018

As of May 2016: 18 countries ⁴	As of June 2017: 39 countries ⁴	By December 2018: 70 countries
Bangladesh, Benin, Burkina Faso, Burundi, Cameroon, Central African Republic, Cote d'Ivoire, DR Congo, Guinea Conakry, Niger, Rwanda, Senegal, Swaziland, Uzbekistan, Vietnam Under clinical trial: Ethiopia, Mongolia, South Africa (Vietnam)	Countries in the adjacent left except Ethiopia Plus 22 countries 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 31 countries Australia, Belarus, Bhutan, Burma/Myanmar, Cambodia, Costa Rica, DPR Korea, Ethiopia, Georgia, Ghana, Indonesia, Kazakhstan, Kenya, Latvia, Liberia, Malawi, Malaysia, Namibia, Nepal, Nigeria, Paraguay, PITC, Singapore, Sri Lanka, Tanzania, Thailand, Togo, Uganda, Ukraine, Zambia, Zimbabwe

Figure 2. Countries implementing the STR, 2017 and 2018



Legend:

As of June 2017
 As of December 2018

Note: The countries in grey either a) had not yet started STR implementation as of the cut-off dates of the data sources; or b) were not among the countries where STR data were collected by the technical agencies; or c) were unable to participate in the survey or respond to the questionnaire.

C. Countries with capacity for SL-LPA

The 2017 Triage TF reported at least 36 countries known to have capacity to perform SL-LPA as of May 2017 (**Table 3**).⁴ DPR Korea was excluded from this list because it had been unable to access LPA

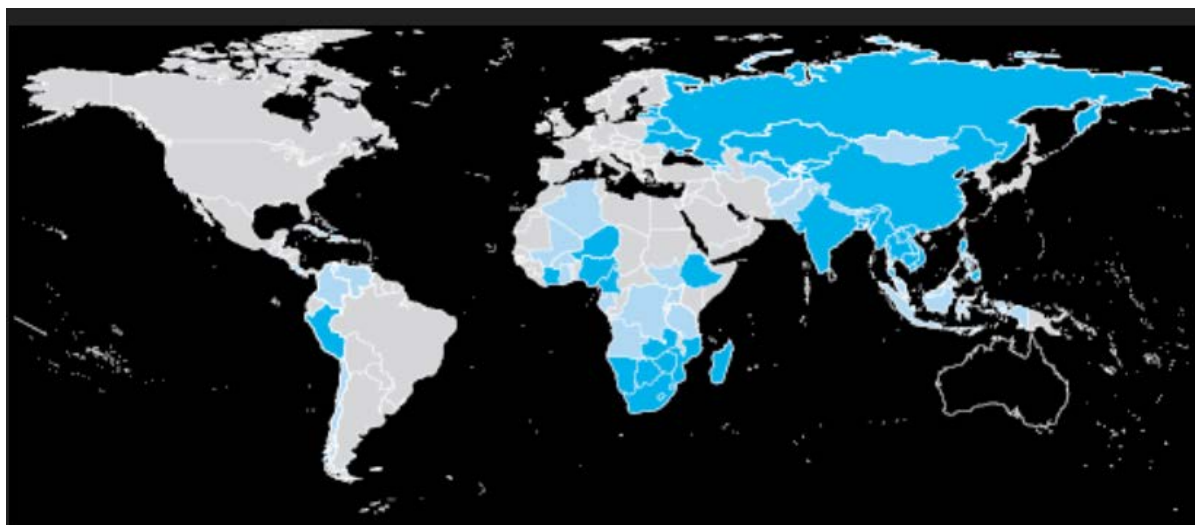
reagents. From 35, this increased to 61 countries as of 2018 (**Table 3**), almost double that in the previous year. A mapping of these 61 countries is shown in **Figure 3**.

As in the STR report, data on SL-LPA do not also show whether the SL-LPA is being done on a research basis or is part of the TB programme’s diagnostic algorithm. Also, countries that were in the planning stage of SL-LPA implementation were not included. Data sources for SL-LPA uptake include the 2017 Triage TF Report,⁴ the WHO survey, and the responses from EMR, SEAR and WPR rGLCs to the TF questionnaire in 2018. CTB also contributed to this list.

Table 3. Countries with capacity for SL-LPA, 2017 and 2018

As of mid-May 2017 : 36 countries ⁴	By June 2018: 61 countries
Armenia, Bangladesh, Belarus, Botswana, Burma/Myanmar, Cambodia, Cameroon, China, Cote d’Ivoire, DPR Korea, Estonia, Ethiopia, Georgia, Haiti, India, Kazakhstan, Kyrgyzstan, Laos PDR, Latvia, Madagascar, Mozambique, Namibia, Niger, Nigeria, Peru, Philippines, Russia, South Africa, Swaziland, Tajikistan, Thailand, Ukraine, Uzbekistan, Vietnam, Zambia, Zimbabwe	Countries on the left column except DPR Korea Plus 26 countries Afghanistan, Algeria, Angola, Azerbaijan, Bhutan, Burkina Faso, Chile, Colombia, Costa Rica, Cuba, DR Congo, El Salvador, Gabon, Ghana, Indonesia, Malaysia, Mali, Mongolia, Nepal, Pakistan, Rwanda, South Sudan, Tanzania, Turkmenistan, Uganda, Venezuela

Figure 3. Countries with SL-LPA capacity, 2017 and 2018



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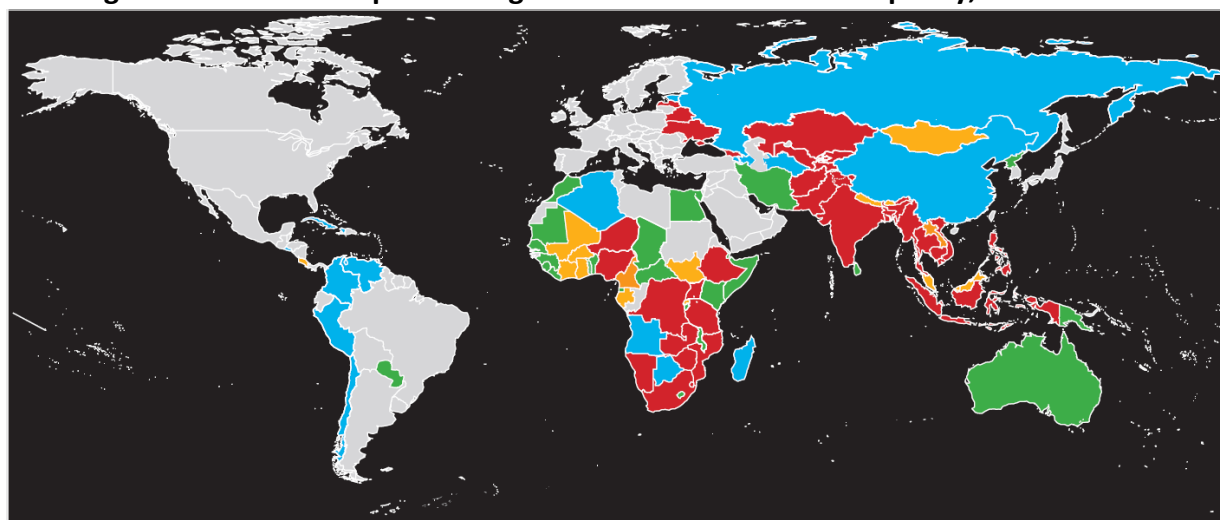
■ As of June 2017 ■ As of December 2018

Note: The countries in grey either a) did not yet have capacity for SL-LPA as of the cut-off dates of the data sources; or b) were not among the countries where SL-LPA data were collected by the technical agencies; or c) were unable to participate in the survey or respond to the questionnaire.

D. Countries at various stages of technology uptake (SL-LPA, STR and the new drugs)

The full triage concept can only be efficiently implemented if the current options for rapid diagnostics and treatment are available in the country. **Figure 4** maps the countries in different stages of technology uptake and **Table 4** enumerates these countries. Countries shaded in red are those that are able to apply the full triage approach, having available in-country the SL-LPA, STR, and the new drugs, Bdq and/or Dlm. There were at least 30 such countries in 2018. Countries shaded in orange are those that have both the SL-LPA and the STR in country, but without the new drugs (14 countries). In green are 26 countries with the STR (\pm Bdq and/or Dlm) but without SL-LPA, while in blue are 17 countries that have the SL-LPA without the STR (\pm Bdq and/or Dlm).

Figure 4. Countries implementing the STR and with SL-LPA capacity, 2017 and 2018



Legend:



Note: The countries in grey either a) had not yet started the SL-LPA, the STR and/or the new drugs as of the cut-off dates of the data sources; or b) were not among the countries where these data were collected by the technical agencies; or c) were unable to participate in the survey or respond to the questionnaire.

Table 4. Countries in different stages of technology uptake

FULL triage (STR, new drugs, and SL-LPA) as of November 2018: 30 countries	
Afghanistan, Bangladesh, Belarus, Burma/Myanmar, Cambodia, Cote d'Ivoire, DR Congo, Ethiopia, Georgia, India, Indonesia, Kazakhstan, Kyrgyzstan, Latvia, Mozambique, Namibia, Niger, Nigeria, Pakistan, Philippines, South Africa, Swaziland, Tajikistan, Tanzania, Thailand, Uganda, Ukraine, Uzbekistan, Vietnam, Zambia, Zimbabwe	
Partial triage (SL-LPA and STR but without the new drugs) as of November 2018: 14 countries	
Bhutan, Burkina Faso, Cameroon, Costa Rica, Cote d'Ivoire, Gabon, Ghana, Laos PDR, Malaysia, Mali, Mongolia, Nepal, Rwanda, South Sudan	
Without SL-LPA, with STR \pm new drug(s): 26 countries	With SL-LPA, without STR, \pm new drug(s): 17 countries

Australia, Benin, Burundi, Central African Republic (RCA), Chad, Djibouti, DPR Korea*, Egypt, Guinea Conakry, Guinea Equatorial, Iran, Kenya*, Lesotho*, Liberia*, Malawi*, Mauritania, Morocco*, Papua New Guinea*, Paraguay, PITC, Senegal, Sierra Leone*, Singapore, Somalia, Sr Lanka, Togo * with Bdq/Dlm	Algeria, Angola, Armenia*, Azerbaijan, Botswana*, Chile, China*, Colombia, Cuba, El Salvador, Estonia*, Haiti*, Madagascar, Peru*, Russia*, Turkmenistan, Venezuela * with Bdq/Dlm
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* 2017 Triage TF Report

Uptake status of the 30 high MDR-TB burden countries

It may not be possible for all countries to take up all the recommended diagnostic and treatment advancements, but countries with the highest DR-TB burden should at least prioritize their implementation. The table below shows the 30 high MDR-TB burden countries (minus the Republic of Moldova where no data were available), with almost 60% able to apply the full triage approach, and the rest with varied capacities. Some countries have shown progress since 2017 based on available data. In 2018, Angola, Azerbaijan, DR Congo, and Pakistan gained capacity for SL-LPA; at least 10 countries started STR implementation, and Indonesia started both SL-LPA and STR.

Table 5. STR and SL-LPA in the high MDR-TB burden countries as of 2018

WHO Region	Full triage (60%): SL-LPA, STR and new drugs	Others
AFR	DR Congo*, Mozambique, Nigeria**, South Africa, Zimbabwe**	Angola* (SL-LPA) Ethiopia** (SL-LPA and Bdq) Kenya** (STR and Bdq)
EUR	Uzbekistan, Kazakhstan**, Kyrgyzstan, Tajikistan	Azerbaijan* (SL-LPA) Belarus** (Bdq, Dlm) Russia (Bdq, Dlm) Ukraine** (Bdq)
EMR	Pakistan*	Somalia (STR)
AMR		Peru (SL-LPA, Bdq)
SEAR	Bangladesh, Burma/Myanmar**, India, Indonesia***, Thailand**	DPR Korea** (STR)
WPR	Philippines, Vietnam	China (Bdq) PNG (STR and Bdq)

*Started SL-LPA in 2018

** Started STR in 2018

*** Started both SL-LPA and STR in 2018

Modifications to the WHO Regimen

Countries that implement modified STR rather than the regimen recommended by WHO in 2016 are listed in **Table 6**.

Table 6. Modifications to the WHO regimen and dosage

Modification to the WHO regimen (and/or dosage)	Country
Bdq instead of Km/Am	South Africa
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
Amikacin (routine) instead of Kanamycin	Burma/Myanmar
Prothionamide all throughout the regimen	Kazakhstan and other CAR countries

Discussion and conclusion

The pace in the uptake of new technology differs from country to country, and is, in most times, dependent on what capacity and competencies are existing and how much work still needs to be done; but political commitment to adapt to change and take on new technology is a huge enabling factor. Before the uptake takes place, advocacy for the new technology is needed to national programs, updating of country policy and guidelines, development of training materials and multi-level staff capacity building, strengthening of existing relevant services in diagnostics and/or treatment and drug safety, forecasting and procurement, recording and reporting, etc. Barriers identified in any of these steps are to be addressed through available program resources or through collaboration with partners on the ground providing technical assistance. Overall, a comprehensive process is needed to integrate change in national programs in a way that will solicit ownership and sustainability, and avoid a transient stand-alone project-based introduction.

Recently, WHO released the new treatment guidelines for MDR-/RR-TB based on the most recent available evidence that signal an important departure from previous approaches to treat MDR/RR-TB.⁸ Fully oral regimens are favored for most patients, with the FQ, Bdq and linezolid strongly recommended as priority drugs in a longer regimen, together with other medicines ranked by a relative balance of benefits to harms. Even as we approach this era of new treatment regimens, with more stringent criteria

⁸ World Health Organization. WHO treatment guidelines for multidrug- and rifampicin-resistant-tuberculosis 2018 update (pre-final text), WHO/CDS/TB/2018.15. WHO-Geneva

and requirements, the triage concept will remain to be an applicable and sound approach to guide and ensure that every patient is given the most appropriate and least toxic regimen.

This report has attempted to gather available information as of December 2018, without including indicative numbers and plans for 2018-2020 to avoid overestimation. Hence, the figures are definitely underestimates, and should be taken with this background in mind. In summary, STR enrolment increased 5X from 2016-2018. The number of countries implementing the STR almost doubled (39 to 70), and so did those with SL-LPA capacity (35 to 61). At least 30 countries are able to apply full triage with the SL-LPA, STR and the new drug(s) in place, and 60% of the 30 high MDR-TB burden countries. To date, however, apart from *ad hoc* one-time surveys and questionnaires, there remains to be no systematic data collection on country implementation of the SL-LPA and the STR. Moreover, among the countries that have information, the scope of the implementation is unknown, whether this is in the pilot or a nationwide scale, or whether this is for research purposes or part of a national diagnostic or treatment algorithm.

With yet another change in the recommendations for RR-/MDR-TB treatment presented to countries, lessons learned from past technology uptake will guide its introduction and integration into TB programs. Technical partners led by WHO need to discuss a harmonious way forward in continuing data collection regarding technology uptake without imposing undue burden on countries. However, beyond enrolment and implementation numbers, treatment outcomes of the various regimens need to be analyzed in order to show the impact these advances have in saving lives.

Acknowledgment

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Mapping by Tristan Bayly, KNCV Tuberculosis Foundation*