World Health Organization

REGIONAL OFFICE FOR Europe

Strengthening pharmacovigilance in the tuberculosis programme in Kyrgyzstan

Report of the technical assistance mission of the WHO Regional Office for Europe

1–5 July 2019

Abstract

Tuberculosis (TB) is one of the key public health issues in Kyrgyzstan. Kyrgyzstan is one of the 27 countries in the world with a high burden of multidrug-resistant tuberculosis (MDR-TB) and is one of the 18 high-priority countries for tuberculosis (TB) in the WHO European Region. In recent years, the Ministry of Health (MoH) of Kyrgyzstan has made progress in putting into effect the National Tuberculosis Programme (NTP), implementing the Global Fund grant and developing the national pharmacovigilance (PV) system. Nonetheless, the TB mortality rate is still the highest in the region (12 per 100 000). The rate of MDR-TB is still high at 22.4% among new cases and 50.2% among retreatment cases. Treatment success was only 53.2% for the MDR-TB cohort and 14.7% for the XDR-TB as of 2016, and the mortality rate was 23.5% for XDR-TB patients. Given this background, there is political will, expressed by the MoH, to introduce and implement the new TB drugs in the country. Since 2017, the NTP, with support of the main partners in the country (the Global Fund, KNCV, MSF), has started to implement use of the new TB drugs in the (pre)XDR-TB treatment regimens with adaptations of routine practice for ensuring the WHO requirements for the use of the new anti-TB drugs such as bedaquiline (Bdq) and delamanid (Dlm). Significant work has been done by the MoH, NTP and partners to ensure the possibility of proper safety monitoring of MDR-TB patients. The country is continuously improving the performance of the TB Control Programme through changes in policy, structure and care, such as the initiation of the use of new drugs, shifting the model of TB care from hospital-based care to a patient-centred model of outpatient care, and making changes in the financing mechanisms for inpatient facilities. Hence, further support from WHO in this process is crucial. In this regard, the MoH has requested that the WHO Regional Office for Europe provides an external evaluation of the National TB Programme, and the achievements it has made since the previous review mission, and makes recommendations for a set of coherent and prioritized actions for further improvements. During the comprehensive NTP review in Kyrgyzstan, carried out in 1 to 9 July, active drug safety monitoring and management (aDSM) and pharmacovigilance of TB drugs was evaluated. Progress and sustainability were assessed in implementing: 1) elements of aDSM, with a focus on the new drugs, within the NTP; and 2) the national PV system. Technical assistance was also provided, with recommendations made on optimizing patient management, recording and reporting adverse drug reactions (ADRs), safety data monitoring and analysis, and signal management activity.

Keywords

PUBLIC HEALTH

ACTIVE DRUG SAFTY MONITORING

PHARMACOVIGILANCE

TUBERCULOSIS

KYRGYZSTAN

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Acknowledgements

The members of the mission would like to express their sincere gratitude to the highest authorities of the Ministry of Health for providing the delegation with the necessary facilities and personnel for successful conduct of the mission.

We particularly thank the following individuals:

- Dr Abdullat Kadyrov, Director of the National Centre of Phthisiology, Ministry of Health, Kyrgyz Republic;
- Gulmira Shakirova, Director of the Department for Drug Provision and Medical Devices, Ministry of Health, Kyrgyz Republic.

The members of the mission express sincere appreciation and gratitude to Dr Jarno Habicht and Dr Saltanat Moldoisaeva, WHO Country Office in Kyrgyzstan, for facilitating the organization of various meetings and visits.

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Abbreviations

ADR	adverse drug reaction
aDSM	active drug safety monitoring
AE	adverse event
Bdq	Bedaquiline
Dlm	Delamanid
DDPMD	Department for Drug Provision and Medical Devices
DR-TB	drug-resistant tuberculosis
GFATM	Global Fund to Fight AIDS, Tuberculosis and Malaria
GVP	good pharmacovigilance practice
HCP	health care provider
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
ICSR	individual case safety report
KNCV	KNCV Tuberculosis Foundation
Lzd	linezolid
MAH	marketing authorization holder
MDR-TB	multidrug-resistant tuberculosis
MHIF	Mandatory Health Insurance Fund
MoH	Ministry of Health
MSF	Médecins Sans Frontières
NCP	National Centre of Phthisiology
NPC	National Pharmacovigilance Centre
NTP	National Tuberculosis Programme
PHC	Public Health Centre
PV	Pharmacovigilance
SAE	serious adverse event
SAR	serious adverse reaction
SmPC	summary of product characteristics
SOP	standard operating procedure
STR	short treatment regimens
TB	Tuberculosis
USAID	United States Agency for International Development
XDR-TB	extensively drug-resistant tuberculosis

Executive summary

Tuberculosis (TB) is one of the key public health issues in Kyrgyzstan. Kyrgyzstan is one of the 27 countries in the world with a high burden of multidrug-resistant tuberculosis (MDR-TB) and is one of the 18 high-priority countries for TB in the WHO European Region. The Ministry of Health (MoH) of Kyrgyzstan has made good progress in putting into effect the National Tuberculosis Programme (NTP) in the country, implementing the Global Fund grant and developing the national pharmacovigilance (PV) system. Nonetheless, the TB mortality rate is still the highest in the region (12 per 100 000). The rate of MDR-TB among new cases was 22.4%; and was 50.2% among retreatment cases as of 2017. Treatment success was only 53.2% for the MDR-TB cohort and 14.7% for the XDR-TB cohort as of 2016, and the mortality rate was 23.5% for XDR-TB patients.

Given this background, there is political will, expressed by the MoH, to introduce and implement the new TB drugs in the country. Since 2017, the NTP, with support of the main partners in the country (the Global Fund, KNCV, MSF), has started to implement use of the new TB drugs in the (pre)XDR-TB treatment regimens with adaptations of routine practice for ensuring the WHO requirements for the use of the new anti-TB drugs such as bedaquiline (Bdq) and delamanid (Dlm). Significant work has been done by the MoH, NTP and partners to ensure proper safety monitoring for MDR-TB patients. The country is continuously improving the performance of the TB Control Programme through changes in policy, structure and care, such as the initiation of the use of new drugs, shifting the model of TB care from hospital-based care to a patient-centred model of outpatient care, and making changes in the financing mechanisms for inpatient facilities. In this regard, the MoH has requested that the WHO Regional Office for Europe provides an external evaluation of the National TB Programme, and the achievements it has made since the previous review mission, and makes recommendations for a set of coherent and prioritized actions for further improvements. During the comprehensive NTP review in Kyrgyzstan, carried out in 1 to 9 July, active drug safety monitoring and management (aDSM) and pharmacovigilance of TB drugs was evaluated.

Essential WHO requirements for introducing new anti-TB drugs include careful monitoring of treatment safety, and management and reporting of adverse drug reactions (ADRs). This requires introduction of a basic framework for establishing aDSM for new anti-TB drugs and monitoring drug resistance.

During a 5-day assessment, mission members met relevant stakeholders and used their findings to provide comprehensive technical assistance. In accordance with the objectives of the mission, the following activities were performed:

- in-country assessment of the fulfilment of WHO requirements for new anti-TB drug applications and patient safety monitoring;
- assessment of progress made towards implementing aDSM elements and pharmacovigilance within the NTP and the national PV system, following the start of a new anti-TB drug application; and
- technical assistance with recommendations made on optimizing patient management, recording and reporting ADRs, safety data monitoring and analysis, and signal management activity.

The current status of aDSM, focused on the new drugs, was assessed at selected inpatient and outpatient settings, where patients with drug-resistant TB (preXDR/XDR-TB) patients are enrolled on treatment with Bdq- and Dlm-containing regimens.

The current national clinical guidelines have been updated to include the recommendations for safety monitoring of the new anti-TB drugs, patient management and AE reporting according to WHO

requirements; this provides the legal and reference basis for the safety monitoring of new and repurposed anti-TB drugs. However, several discrepancies were noted in safety monitoring recommendations, compared with WHO minimum essential requirements for appropriate safety monitoring parameters of the new TB drugs, that should be addressed in the next clinical guideline review. The updated version of the national TB clinical guidelines are based on the WHO Consolidated Guidelines on Drug-Resistant Tuberculosis Treatment, 2019[1] and are at the final stage of development. The full scope of the current recommendations for the treatment of patients with MDR-TB, including the specific requirements for aDSM, are intended to be included in these guidelines. Statutory provision for PV and aDSM activity is implemented in the country: ADR reporting policy and requirements are stipulated in the PV national legislation at the country level and are addressed as part of the obligatory aDSM requirements in national TB clinical guidance. Indicators of AE reporting activity are included in the NTP programme indicators, and could be considered as an additional supportive tool for the implementation of a sustainable reporting system in NTP.

In the main, clinical, diagnostic and laboratory facilities were available at the hospital settings visited (National TB Centre, Kara-Balta TB hospital) for regular monitoring of patient safety in line with current WHO recommendations; however, some clinical settings still have difficulties with the availability and/or performance of all the required tests/examinations (e.g. the hospital in Archaly). The TB cabinets in Family Medicine Centres that are responsible for the management of patients at the outpatient stage have different levels of equipment and resources available for meeting the specific requirements for patient safety monitoring, with the most common limitations involving serum electrolytes and albumin monitoring. The TB cabinets in Bishkek and the regional Family Medicine Centres have the capacity to monitor cardiological and biochemical safety parameters. To maintain essential laboratory testing, including serum electrolytes and albumin, in 2018 a special order was approved by the MoH and the Mandatory Health Insurance Fund (No. 626 of 30 August 2018) to ensure the provision of laboratory diagnostics by private diagnostic laboratories in the absence of the appropriate laboratory capacity in the health care facilities. The introduction of this mechanism has allowed significantly increased patient access to essential safety monitoring. For patients who continue to receive anti-TB therapy with injectables, in practice there is no opportunity for audiometry to be performed in most facilities, which continues to be a significant limitation in providing patients with the proper conditions for monitoring treatment safety in respect to disabling adverse effects, such as ototoxicity.

Significant work has been done by the NTP and partner organizations to implement the new essential safety monitoring and management element into routine clinical and outpatient practice. Health care providers (HCPs) in the National TB Control Centre and regional TB cabinets are aware of the recommendations for the additional elements of safety monitoring for DR-TB treatment safety. The practice of members of the Central Concilium conducting field consultations to provide local assistance, as well as monitoring the management of patients undergoing treatment with the new and repurposed TB drugs and in STR, together with the coordinators of KNCV, has been implemented in the country.

In order to optimize monitoring, individualized and treatment-adapted regimen safety monitoring sheets have been developed and introduced into practice; these individualized monitoring sheets are included in the patient's medical records. These monitoring sheets allow clinicians to have an overview of trends over time; for example, QTcF intervals, haemoglobin levels etc. The recording and clinical management

[1] WHO. WHO consolidated guidelines on drug-resistant tuberculosis treatment. Geneva: World Health Organization; 2019. (https://www.who.int/tb/publications/2019/consolidated-guidelines-drug-resistant-TB-treatment/en/, accessed 25 September 2019).

based on the test results has substantially improved. Primary care specialists (HCPs in Family Medicine Centres and Family Medicines Groups) are informed of the mandatory referral of the patient to a responsible TB specialist if there is any suspicion of an adverse reaction. Additional training for HCPs in Family Medicine Centres and Family Medicines Groups on the recommendations for essential safety monitoring of MDR-TB patients could be considered.

An intensive training campaign for HCPs was held in the country with the support of the partners for safety monitoring and management of AEs in DR-TB patients. HCPs are aware of risk of AEs and AE management recommendations. However, in some cases, systematic performance of safety management in practice has limitations with respect to safety monitoring data analysis, deviations detection and carrying out the recommended AE management. In many cases the results of the investigations performed are not evaluated, the appropriate measures for ADR management are not taken, or the measures taken are not correct, including cases of serious ADRs. There are occasional interruptions in the availability of some medicines used for the management of ADRs.

Significant work has been done by the NTP, the National Pharmacovigilance Centre (NPC) and partners to implement pharmacovigilance and AE reporting into routine practice. AE reporting practice has been introduced into the NTP starting from the implementation of new drugs and regimens for DR-TB treatment. Intensive training programme for methodology of AE reporting and assessment have been conducted countrywide, specialists from the NTP responsible for PV have been appointed in every region, and standard operation procedures (SOPs) for AE reporting have been developed and implemented. The national TB clinical guidelines contain a strategy for defining an intermediate package as a target monitoring and AE reporting model within aDSM activity.

HCPs are aware of AE reporting requirements and are trained in methodology. AEs are collected by the responsible person for pharmacovigilance in the National Centre of Phthisiology, evaluated and submitted in the NPC. For the period 2017–2018, the total number of reported ADR increased almost three times.

The NPC was re-established as a separate department in the Department for Drug Provision and Medical Devices (DDPMD) in 2015. Since its establishment, the Centre's management and pharmacovigilance specialists have actively worked on the introduction and development of the national pharmacovigilance and ADR reporting systems. The NPC unit employs three full-time specialists with medical educations, the required level of competence and technical expertise.

Governance and political commitment at government and MoH level has been provided for implementing pharmacovigilance and good pharmacovigilance practice in national legislation and regulatory practice, which is a significant achievement in the development of the pharmacovigilance system in the country. The pharmacovigilance system has a statutory provision stipulated in the Law on Medicines of the Republic of Kyrgyzstan No. 165 (adopted 2 August 2017) and in by-law regulations. Legislation on good pharmacovigilance practices (GVP) came into force in December 2018 as part of the Eurasian Economic Union regulation ("Good Pharmacovigilance Practices in the Eurasian Economic Union" approved by the Board of the Eurasian Economic Union Commission Decree No 87, issued 3 November 2016).
ADR reporting forms, including an online ADR reporting form, are available on the official site of the DDPMD, and paper forms are available in health care facilities. A special interactive programme for patient online ADR reporting has been introduced by NPC in cooperation with Uppsala Monitoring Centre.

Critical PV procedures for collecting, recording and analysing ADR reports are regularly performed. PV processes, including continuous safety data monitoring and signal management, are undergoing further improvement. Since the introduction of the new anti-TB drugs into the treatment regimens, the data received on safety concerns have been consistent with the expected safety profiles of the monitored anti-

TB drugs. Establishing a more effective interaction with the NTP to ensure appropriate aDSM ADR data evaluation, causality assessment, signal detection and management is recommended.

Given these achievements and opportunities for further improvement, the mission recommends the following actions:

Recommendations	**Main responsible party**
Update the National TB Clinical guideline on drug-resistant tuberculosis treatment for further harmonization with the latest WHO recommendations on essential safety monitoring requirements and AE management for new and repurposed anti-TB drugs.	MoH, NTP
Perform additional evaluation of the safety monitoring practice in hospital and outpatients settings with mapping of the gaps and considering the optimal way for further adaptation of resources, updating of knowledge, adaptation of finance planning and procurement of laboratory reagents for sustainable implementation of safety monitoring requirements.	NTP
Consider the option of addressing the limitations of order No 626, of 30 August 2018 from the MoH and MHIF, with respect to the limited number of tests that could be performed annually.	NTP, MoH, MHIF
Consider effective measures for further implementation of sustainable safety monitoring and management into routine practice with the involvement and supportive supervision of MDR-TB and PV local coordinators, systematic monitoring of treatment safety management practice on clinical and outpatient settings, and additional local training sessions.	NTP
Consider further adaptation of medicine procurement planning for the requirement of medicines for ADR management: detect gaps, re-evaluate requirements and available resources, and correct an application when necessary.	NTP
Ensure regular and timely reporting of SAEs and AEs of special interest experienced by the NTP to the NPC according to WHO recommendations. Consider the potential of supporting specialists at the MoH level, to eliminate the risk of punishment in case of SAE reporting.	NTP, MoH
Establish more effective interaction with the NTP to ensure appropriate aDSM ADR data assessment, signal detection and management by forming an NTP–NPC safety surveillance committee.	NPC, NTP
Consider incorporating an ADR recording module into the e-TB manager to optimize safety data recording, evaluation and clinical management.	NTP
Consider establishing compatibility between the e-TB manager and the national ADR database to optimize ADR reporting.	NTP, partners
Ensure access for HCPs to the updated ADR reporting form.	NPC
Ensure submitting AE data received by the NPC within implemented aDSM in NTP to the specialized WHO aDSM global database.	NPC
Update the monitoring schedule and data collection forms to reflect changes in the WHO DR-TB guidelines 2019.	NTP

1 Background

Tuberculosis (TB) is one of the key public health issues in Kyrgyzstan. Kyrgyzstan is one of the 27 countries in the world with a high burden of multidrug-resistant tuberculosis (MDR-TB) and is one of the 18 high-priority countries for TB in the WHO European Region. The Ministry of Health (MoH) of Kyrgyzstan has made good progress in putting into effect the National Tuberculosis Programme (NTP) in the country, implementing the Global Fund grant and developing the national pharmacovigilance (PV) system. Nonetheless, the TB mortality rate is still the highest in the region (12 per 100 000). The rate of MDR-TB among new cases was 22.4%; and was 50.2% among retreatment cases as of 2017. Treatment success was only 53.2% for the MDR-TB cohort and 14.7% for the XDR-TB cohort as of 2016, and the mortality rate was 23.5% for XDR-TB patients.

Given this background, there is political will, expressed by the MoH, to introduce and implement the new TB drugs in the country. Since 2017, the NTP, with support of the main partners in the country (the Global Fund, KNCV, MSF), has started to implement use of the new TB drugs in the (pre)XDR-TB treatment regimens with adaptations of routine practice for ensuring the WHO requirements for the use of the new anti-TB drugs such as Bdq and Dlm. Significant work has been done by the MoH, NTP and partners to ensure proper safety monitoring for MDR-TB patients. The country is continuously improving the performance of the TB Control Programme through changes in policy, structure and care, such as the initiation of the use of new drugs, shifting the model of TB care from hospital-based care to a patient-centred model of outpatient care, and making changes in the financing mechanisms for inpatient facilities. In this regard, the MoH has requested that the WHO Regional Office for Europe provides an external evaluation of the National TB Programme, and the achievements it has made since the previous review mission, and makes recommendations for a set of coherent and prioritized actions for further improvements. During the comprehensive NTP review in Kyrgyzstan, aDSM and pharmacovigilance of TB drugs and consumables was evaluated. Progress and sustainability were assessed in the implementation of: 1) elements of aDSM and management, with a focus on new drugs, within the NTP; and 2) the national PV system.

Essential WHO requirements for introducing new anti-TB drugs include careful monitoring of treatment safety, and management and reporting of adverse drug reaction (ADRs). This requires introduction of a basic framework for establishing aDSM for new anti-TB drugs and monitoring of drug resistance. Under the overarching umbrella of the new anti-TB drug introduction, it is essential to achieve close coordination of aDSM activities with the main PV structures at country level, together with further development of signal detection capacity.

2 Objectives of the mission

The two main objectives were to perform:

1) an in-country assessment of progress in fulfilling WHO requirements and readiness for implementation of new anti-TB drug and patient safety monitoring;

2) an assessment of progress made in implementing aDSM elements within the NTP and the national PV system.

Tasks

The main tasks were:

1) to assess the current status of aDSM implementation in TB practice, with a focus on new anti-TB drugs, in order to identify gaps in system performance and to provide recommendations to the NTP/MoH on making best use of existing platforms and entities to maximize efficiency;

2) to assess the current status of the national PV system and of PV activity with the focus on aDSM elements;

3) to provide technical assistance with recommendations on optimizing patient management, recording and reporting adverse drug reactions (ADRs), safety data monitoring and analysis, and signal management activity.

3 National PV system: progress in developing the core structure

3.1 NPC structure and statutory provision of PV activity

Statutory provision of PV activity has been implemented. Important steps have been taken towards implementing legislation: amendments to the Law of Medicines stipulating a national PV policy were made and come into force in February 2018. Pharmacovigilance system statutory provision was included in the Law on Medicines of the Republic of Kyrgyzstan No. 165 (adopted 2 August 2017).

Legislation on good pharmacovigilance practices (GVP) came into force in December 2018 as part of the Eurasian Economic Union regulation Good Pharmacovigilance Practices in the Eurasian Economic Union" approved by the Board of the Eurasian Economic Union Commission Decree No. 87, issued 3 November 2016. This means that the recommendation to finalize the development of detailed by-laws on PV regulation, including the implementation of GVP requirements, has been fulfilled. By-laws on PV regulation were finalized and have come into force (Decree No. 564 of 6 December 2018 approving the requirements to organization and functioning of pharmacovigilance system).

In 2015 the National Pharmacovigilance Centre (NPC) was re-established as a separate department in the Department for Drug Provision and Medical Devices (DDPMD). Since its establishment, the Centre's management and PV specialists have actively worked on the introduction and development of national PV and the national ADR reporting system. The NPC unit employs three full-time specialists with medical educations, the required level of competence and technical expertise.

3.2 ADR reporting form

The national ADR reporting form (the so-called yellow card) was implemented in 2014; a revised version of the form has been available since 2018. The form includes the relevant sections required to collect essential data for evaluating ADR report validity and causality assessment. The ADR reporting form allows the recording of information on suspected medication errors, suspected counterfeit/substandard medicines, therapeutic ineffectiveness, and suspected misuse/abuse of and dependence on medicines.

ADR reporting forms, including the online ADR reporting form, are available on the official site of the DDPMD, paper forms are available in health care facilities. A special interactive programme for patient online ADR reporting has been introduced by the NPC in cooperation with Uppsala Monitoring Centre.

In the country significant work has been done to implement the procedure of patients reporting ADRs. Special interactive programmes for patient online ADR reporting has been introduced by the NPC in cooperation with Uppsala Monitoring Centre.

Recommendations:

- ensure access for HCPs to the updated ADR reporting form.

3.3 ADR collection and analysis with continuous aDSM within the national PV system framework

Routine NPC activities include collecting, processing, recording and analysing ADR reports; follow-up on missing information; duplicate detection; and integrated quality control. Finalization and approval of appropriate SOPs is recommended. Critical PV processes, including continuous drug safety profile monitoring, signal management and risk–benefit evaluation of authorized medicines, are implemented and are under further improvement. Annually, approximately 4–5 signals are generated and passed for validation on the basis of local ADR data submitted to the NPC. aDSM requirements for SAE reporting have been met, though some limitations in the reporting has been identified. At the time of the assessment, the national ADR database included five SAEs experienced by patients exposed to Bdq or Dlm.

Effective feedback to reporters is provided in oral and/or written forms and includes information on the results of ADR evaluation and planned measures (if any) in the light of ADR report(s) submitted; however, feedback activity should be performed regularly.

Recommendations:

- finalize implementation of SOPs for core PV activity; and
- continue the development of mutual capacity for signal detection with the NTP within the aDSM framework.

3.4 National ADR database

The national ADR database is not currently harmonized with the International Conference on Harmonisation (ICH) E2B recommendations. VigiFlow software (a web-based ADR management system for PV centres, available from the Uppsala Monitoring Centre) is used for the submission of ADRs to VigiBase (WHO's global individual case safety reports (ICSR) database)**.**

Submission of ADR data received from the aDSM implemented in the NTP to the specialized aDSM global database is recommended.

ADR reports are submitted to the WHO global ADR database (VigiBase); the number submitted ICSR tends to increase, so previous recommendation to intensify work towards the WHO global ADR database (VigiBase) reporting has been fulfilled.

Recommendations:

- start submitting ADR data received from the implemented aDSM in the NTP to the specialized aDSM global database; and
- consider upgrading the ICSR database further to meet ICH E2B(R3) requirements.

3.5 Availability of new drug safety information

NPC staff monitor the available international data for new drug safety information, which is analysed regularly. New safety data and changes in current recommendations are placed on the DDPMD website; however, further optimization is required to ensure systematization of information and rapid searches. Placing important information in chronological order with identifying headers is recommended. The

procedures for the systematic provision of new safety information for HCPs, and early amendments to the summaries of product characteristics (SmPCs) has been implemented.

Recommendations:

- to facilitate searching, consider placing all new safety information on the website in chronological order under a special heading "Drug safety" with an identifying header;
- ensure HCPs are regularly informed about new safety data and changes in the current recommendations; consider additional tools to improve HCPs' access to new safety information; and
- ensure that the marketing authorization holders (MAHs) responsible for organizing appropriate PV systems within their networks exchange safety data on drugs that are authorized and released onto the market.

4 Performance of the national PV system: service delivery and information management

4.1 ADR reporting and signal management

Since 2017 there has been a significant increase in the number of ADR reports submitted to the NPC; from 100 ADR reports in 2017 to 306 in 2018, and 176 as of June 2019. The increase in the average reporting rate, from 17 ADR reports per million inhabitants in 2017 to 46 ADR reports per million inhabitants in 2019, represents a positive development in the national ADR reporting system; however, these rates as still lower than the benchmark WHO ADR reporting rate.[2] Approximately 65% of ADR reports were submitted by the NTP for adverse events related to anti-TB drugs. At the time of the mission, the database included approximately 300 ADRs that had been received from the NTP; this demonstrates the leadership of the tuberculosis programme in the national ADR reporting system in Kyrgystan. Currently, ADR data received from the aDSM implemented in the NTP is not submitted to the specialized aDSM global database. Since aDSM has been implemented, five SAEs have been reported for patients exposed to Bdq, which is an indication of insufficient levels of serious adverse event reporting due to HCP fears of subsequent punishment.

The database includes reports of other drug-related problems, such as therapeutic ineffectiveness and suspected substandard medicines. DDPMD management and PV staff regularly undertake a range of comprehensive measures to further increase the level of ADR reporting.

Recommendations:

- to make further efforts to incorporate regular PV in the health care system with the involvement of all stakeholders;
- to strengthen political commitment and governance at government and MoH levels to render support for ADR reporters to improve the situation with SAE reporting; and

[2] WHO. Safety monitoring of medicinal products: guidelines for setting up and running a pharmacovigilance centre. WHO Collaborating Centre for International Drug Monitoring. Uppsala: The Uppsala Monitoring Centre; 2000 (http://apps.who.int/medicinedocs/en/d/Jh2934e, accessed 25 September 2019).

- to make further efforts to motivate HCPs, via managerial support and effective feedback; to provide further promotion and training for ADR reporting activity; and implement active PV programmes.

4.2 Involving the pharmaceutical industry in the PV system

Appropriate legislation with respect to implementing the PV system into the country, including the stipulation of the requirement to marketing authorization holders (MAHs) to implement an appropriate PV system, has been being introduced in the country from December 2018 as part of Eurasian Economic Union regulation ("Good Pharmacovigilance Practices in the Eurasian Economic Union" approved by the Board of the Eurasian Economic Union Commission Decree No. 87, issued 3 November 2016). This regulation includes the full scope of GVP requirements: PV quality systems, including a qualified person for PV requirements and PV audits; requirements for critical PV procedures and PV documents (signal management, ICSR management, a PV master-file, periodic safety update reports, risk management system), PV inspections and audits.

The pharmaceutical industry is aware of and is becoming more responsible for appropriately organizing country's PV system; however, the MAHs responsible are at different levels of development with regard to PV system. The DDPMD is undertaking measures to intensify its control of MAH PV activity and the fulfilment of its responsibilities.

5 aDSM elements in the NTP: policy and practice

The current policy, practice and the resources available have been assessed, with a focus on implementation and sustainability of aDSM and WHO requirements for the use of the new anti-TB drugs. These requirements include local guidelines and clinical protocols, SOPs and primary documentation; human resources; availability of clinical diagnostic and laboratory facilities with appropriate equipment for regular aDSM and monitoring of drug effectiveness in patients; PV knowledge and skills of NTP HCPs; current ADR reporting practices; availability of ADR reporting forms; and current ADR management and risk minimization measures.

5.1 Implementing aDSM in the NTP

Since 2017, the NTP, with support of the main partners in the country (the Global Fund, KNCV, MSF), has started to implement use of the new TB drugs in the (pre)XDR-TB treatment regimens with adaptations of routine practice for ensuring the WHO requirements for the use of the new anti-TB drugs such as Bdq and Dlm. Significant work has been done by the MoH, NTP and partners to ensure proper safety monitoring for MDR-TB patients; the national clinical guidelines have been updated to include WHO aDSM recommendations; countrywide training sessions for HCPs in safety monitoring, management and AE reporting have been carried out; additional monitoring of safety laboratory requirements and functional parameters have been implemented; special legislation has been approved to ensure the provision of laboratory diagnostics by private diagnostic laboratories in the absence of appropriate laboratory capacity in the public health care facilities.

5.2 Current status of aDSM in the NTP

The current national clinical guidelines have been updated to include the recommendations for safety monitoring of the new anti-TB drugs, patient management and AE reporting according to WHO requirements; this provides the legal and reference basis for the safety monitoring of new and repurposed anti-TB drugs. However, there are several discrepancies in the safety monitoring recommendations

compared with the WHO minimum essential requirements for appropriate safety monitoring parameters of new TB drugs (with regard to serum potassium, platelet count, albumin, lipase) that should be addressed in the next clinical guideline review. AE management recommendations specific to the new and repurposed TB drugs are not included in the current clinical guideline; HCPs in their practical activity are based on clinical recommendations provided by the partners, which comply with WHO recommendations. The updated version of the national TB clinical guidelines are based on the WHO Consolidated Guidelines on Drug-Resistant Tuberculosis Treatment, 2019[3] and are at the final stage of development (review by MoH). The full scope of the current recommendations for the treatment of patients with MDR-TB, including the specific requirements for aDSM, are intended to be included in these guidelines. Statutory provision for PV and aDSM activity is implemented in the country: ADR reporting policy and requirements are stipulated in the PV national legislation at the country level and addressed as part of the obligatory aDSM requirements in the national TB clinical guidance. Indicators of AE reporting activity are included in the NTP programme indicators, and could be considered as an additional supportive tool for the implementation of a sustainable reporting system in NTP.

Countrywide Bdq and Dlm treatment started in 2017. As of 2018, 684 RR/MDR-TB patients have been enrolled on treatment with the new and repurposed anti-TB drugs. Patient enrolment for treatment with the new anti-TB drugs is determined by the Central and regional consiliums.

5.2.1 Systematic clinical and laboratory assessment

In the main, clinical, diagnostic and laboratory facilities were available at the hospital settings visited (National TB Centre, Kara-Balta TB hospital, several districts) for regular monitoring of patient safety in line with current WHO recommendations; however, some clinical settings still have difficulties with the availability and/or performance of all required tests/examinations (e.g. hospital in Archaly, Jalalabad Oblast TD MDR ward). The TB cabinets in Family Medicine Centres that are responsible for the management of patients at the outpatient stage have different levels of equipment and resource availability for meeting the specific requirements for patient safety monitoring, with the most common limitations related to serum electrolytes and albumin monitoring. The TB cabinets located in Bishkek and the regional Family Medicine Centres have the capacity to monitor cardiological and biochemical safety parameters. It should be noted that, since January 2019, all safety monitoring examinations are financed from the Mandatory Health Insurance Fund. In 2018, to enable all essential laboratory testing to be carried out, including serum electrolytes and albumin, a special order was approved by the MoH and the Mandatory Health Insurance Fund (No 626 of 30 August 2018) to ensure the provision of laboratory diagnostics by private diagnostic laboratories in the absence of the appropriate laboratory capacities in health care facilities. The introduction of this mechanism has allowed significantly increased patient access to essential safety monitoring. To improve the safety monitoring system further, several limitations of this mechanism should be addressed: the periodicity of albumin monitoring does not meet the WHO recommendation (4 times per year); the fixed number of laboratory tests for all other parameters makes it impossible to perform monitoring when the use of new TB drugs is extended, or when unscheduled monitoring is required in cases of detection of adverse changes in the patient's condition. Additionally, the capacity or available mechanisms in outpatient settings to provide patients with the appropriate laboratory and diagnostic safety monitoring in accordance with the WHO requirements for the management of patients treated with new anti-TB drugs should be re-assessed with involvement of the

[3] WHO. WHO consolidated guidelines on drug-resistant tuberculosis treatment. Geneva: World Health Organization; 2019. (https://www.who.int/tb/publications/2019/consolidated-guidelines-drug-resistant-TB-treatment/en/, accessed 25 September 2019).

family medicine groups and the feldsher obstetric centres. For patients who continue to receive anti-TB therapy with injectables, there is no opportunity in practice for audiometry to be performed in most facilities continues to be a significant limitation in providing patients with the proper conditions for monitoring treatment safety in respect of disabling adverse effects, such as ototoxicity.

Significant work has been done by the NTP and partner organizations to implement the new essential safety monitoring and management element into routine clinical and outpatient practice. HCPs in the National TB Control Centre and regional TB cabinets are aware of the recommendations for the additional elements of safety monitoring for DR-TB treatment safety. The practice of conducting field consultations by members of the Central Concilium for the provision of local assistance, as well as monitoring the management of patients undergoing treatment with the new and repurposed TB drugs and in STR, together with the coordinators of KNCV has been implemented in the country.

In order to optimize monitoring, individualized and treatment-adapted regimen safety monitoring sheets have been developed and introduced in the practice; these individualized monitoring sheets are included in the patient's medical records. These monitoring sheets allow clinicians to have an overview of trends in time; for example, QTcF intervals, haemoglobin levels etc. The recording and clinical management based on tests results has substantially improved. A report on the timeliness and results of the tests of patients with DR-TB who are being treated with new and repurposed TB drugs and STR, is submitted monthly by the regional coordinators for DR-TB in the NCP. Currently, in each region where such patients are available, assistance in their management is provided by the staff of the "Challenge TB" project. At the end of the project, it is expected that district phthisiatricians (TB physicians) will assist in collecting data.

However, since these monitoring sheets are not routinely filled out in some cases (as some facilities or some clinicians are not fully following the protocol), or contain different data, further efforts are required to introduce this tool into routine clinical practice, including in outpatient settings. The monitoring tool should also be updated based in changes in treatment regimen in accordance with the WHO DR-TB 2019 guidelines, and should include space for additional monitoring tests; for example, polyneuropathy tests, as Lzd will be used for the majority of patients. If there are deviations from the monitoring schedule, these are mostly associated with restrictions on access (lack of reagents, breakdown of equipment, inability to transport samples, etc.), so the responsibilities and management at the local level should be strengthened to prevent and eliminate these risk factors for the safety management system. Primary care specialists (HCPs in Family Medicine Centres and Family Medicines Groups) are informed of the mandatory referral of the patient to a responsible TB specialist if there is any suspicion of an adverse reaction. Additional training for HCPs in the Family Medicine Centres and Family Medicines Groups on the recommendations for essential safety monitoring of MDR-TB patients could be considered.

5.2.2 Management of ADRs

With the support of the main partners, an intensive training campaign was held in the country for HCPs on safety monitoring and management of AEs in DR-TB patients. HCPs are aware of the risk of AEs and the AE management recommendations. However, in some cases, systematic performance of safety management in practice has limitations with respect to safety monitoring data analysis, deviations detection and carrying out the recommended AE management. During the visits to clinical facilities, it was noticed that abnormal test results are frequently not followed up, are not properly managed or are not managed at all. For example, there were patients, including children with QTcF prolongation >500, for whom there were no relevant actions taken by clinicians.

Medicines for the treatment of ADRs, in the main, are available in the clinical settings. Additional measures to ensure an uninterrupted supply of medicines for the management of ADRs (especially for electrolyte replacement medicines for oral and parenteral use) related to the new and repurposed anti-TB drugs need to be considered.

5.2.3 ADR recording and reporting

Significant work has been done by the NTP, the NPC and partners to implement PV and AE reporting into routine practice. AE reporting practice has been introduced in the NTP starting from the implementation of the new drugs and regimens for DR-TB treatment. Intensive training programmes for AE reporting methodology and assessment have been conducted countrywide, specialists from NTP responsible for PV have been appointed in every region, and SOPs for AE reporting have been developed and implemented. The national TB clinical guidelines contain a strategy for defining an intermediate package as a target monitoring and AE reporting model within the aDSM activity. Medical records of MDR-TB patients (TB01) include a section designed to record ADRs experienced by patients; however, recording is not carried out systematically.

HCPs are aware of AE reporting requirements and are trained in methodology. AEs are collected by the responsible person for PV in the National Centre of Phthisiology, evaluated and submitted to NPC. From 2017 to 2018, the total number of reported ADRs has increased almost three times. Approximately 65% of the AEs collected by the NPC annually are submitted by the NTP, which is a significant achievement for the first implemented system. However, there are significant limitations in the reporting of serious AEs and AEs of special interest; more than half of submitted AEs represent mild gastrointestinal disorders. AEs related to the new anti-TB drugs are minimally reported, which results in minimal effectiveness of the ADR reporting system with respect to signal detection. The quality of some of the AE reports that are submitted is suboptimal in that not all essential information is included, which requires intensive follow-up on the part of the PV-responsible NTP staff member. The AE reporting practice within an aDSM framework should be further developed to be more effective in collecting important safety data, SAEs and AEs of special interest.

Recommendations:

- Update the national TB clinical guidelines on DR-TB treatment so that they reflect the latest WHO recommendations on essential safety monitoring requirements and AE management for the new and repurposed anti-TB drugs.
- Perform additional evaluation of safety monitoring practices in hospitals and outpatients settings, map the gaps in practice and consider the optimal way to further adapt resources, update knowledge, adapt the finance planning and the procurement of laboratory reagents to enable a sustainable implementation of the safety monitoring requirements. Consider the opportunity to address the limitations of the order No. 626 of 30 August 2018 of the MoH and MHIF with regard to the limited number of tests can be performed annually.
- Consider effective measures for further implementing sustainable safety monitoring and management into routine practice, with the involvement and supportive supervision of MDR-TB and PV local coordinators, the systematic monitoring of treatment safety management practice on clinical and outpatient settings, and additional local training sessions.
- Consider further adaptation of medicines procurement planning to requirement in medicines for ADR management: detect gaps, re-evaluate requirements and available resources, and correct applications when necessary.

- Ensure regular and timely reporting of SAEs and AEs of special interest, identified by the NTP, to the NPC according to WHO recommendations. Consider the possibility of supporting specialists at the MoH level to eliminate the risk of punishment in cases of SAE reporting.
- Establish more effective interaction with the NTP to ensure appropriate aDSM ADR data assessment, signal detection and management by forming an NTP–NPC safety surveillance committee.
- Consider incorporating an ADR recording module into the e-TB manager to optimize safety data recording, evaluation and clinical management.
- Consider establishing compatibility between the e-TB manager and the national ADR database to optimize ADR reporting.
- Update the monitoring schedule and data collection forms to reflect changes in WHO DR-TB guidelines 2019.