World Health Organization
REGIONAL OFFICE FOR Europe

Meeting of the European Laboratory Initiative (ELI) on TB, HIV and Viral Hepatitis Core Group

Copenhagen, Denmark
1-2 November 2018

Abstract

The European Laboratory Initiative (ELI) on TB, HIV and Viral Hepatitis meeting was conducted by ELI and its Secretariat at the WHO Regional Office for Europe in Copenhagen, Denmark on 1-2 November 2018. The meeting brought ELI Core Group Members, ELI Advisers, international experts, WHO consultants and WHO Technical officers together in order to strengthen TB, HIV and viral hepatitis laboratory diagnostics, testing and monitoring capacity. The most recent developments in these fields were covered during expert presentations followed by extensive discussions. Panel discussions, roundtable discussions and group discussions were conducted on whole genome sequencing use for TB, HIV and viral hepatitis; algorithm updates; SL-SLPA updates and future directions. The Core Group agreed on ELI future directions, next steps and deadlines.

Keywords
TB
HIV
Viral Hepatitis
Clinical laboratory techniques
Capacity building
Next Generation Sequencing
Whole Genome Sequencing
Algorithms

Address requests about publications of the WHO Regional Office for Europe to:

Publications
WHO Regional Office for Europe
UN City, Marmorvej 51
DK-2100 Copenhagen Ø, Denmark

Alternatively, complete an online request form for documentation, health information, or for permission to quote or translate, on the Regional Office website (http://www.euro.who.int/pubrequest).

any kind, either express or implied. The responsibility for the interpretation and use of the material lies with the reader. In no event shall the World Health Organization be liable for damages arising from its use. The views expressed by authors, editors, or expert groups do not necessarily represent the decisions or the stated policy of the World Health Organization.

Table of Contents

Abbreviations

BSC	biosafety cabinet
CB	clinical breakpoints
DST	drug susceptibility testing
DTG	dolutegravir
EECA	Eastern Europe Central Asia
ELI	European Laboratory Initiative
FL-LPA	first-line line probe assay
GLI	Global Laboratory Initiative
GLC	Green Light Committee
HCV	hepatitis C virus
LMIC	low- and middle-income countries
LPA	line probe assay
MDR-TB	multi-drug resistant tuberculosis
MIC	minimum inhibitory complex
MoH	Ministry of Health
NGS	next generation sequencing
pDST	phenotypic drug susceptibility testing
TB	tuberculosis
RDT	rapid diagnostic test
SL-LPA	second-line line probe assay
XDR-TB	extensively drug resistant tuberculosis
UN	United Nations

Background, scope and objectives

Background

Scaling up laboratory services to meet the diagnostic, testing and monitoring challenges of tuberculosis (TB) and drug-resistant TB as well as TB-HIV co-infection, HIV and viral hepatitis are of key importance within the region and call for a paradigm shift in laboratory diagnostics, testing and monitoring policy development.

TB, and particularly multidrug-resistant TB (MDR-TB), remain major public health concerns in the WHO European Region. Timely and accurate laboratory diagnostic services play a key role in detecting TB and providing patients with appropriate treatment. There is a need to improve TB and MDR-TB detection and expand quality-assured susceptibility testing for second-line drugs. Similarly, rapid TB diagnostic methods need to be efficiently located and applied within laboratory networks which are rationally organized and sufficiently adapted to country contexts. The need for further scale-up of diagnostic laboratory capacity is also highlighted in the regional TB Action Plan (2016–2020), which was endorsed by the WHO Regional Committee for Europe in Vilnius, Lithuania in September 2015.

In response to this need, the European Laboratory Initiative (ELI) was established to scale up primarily TB diagnostic capacity. From 2018 onwards ELI's mandate has expanded to cover laboratory diagnostics, testing and treatment monitoring needs of HIV and viral hepatitis as well. The rationale behind this decision is primarily based on the following points, i) WHO European Region being the only region globally with rising HIV infections thus consequently also increasing TB-HIV co-infections with late stage diagnosis, ii) viral hepatitis remaining a dominant public health threat within the region with only around 30% of people living with chronic hepatitis C and less than 20% of those with chronic hepatitis B having been diagnosed in 2015.

At the same time laboratory methods for diagnostics and treatment monitoring have advanced rapidly in the recent years for all three diseases, while addressing these diseases remained in vertical systems, with little to no integration. Therefore, the aim of ELI is to explore all technological and countries' capacities for the better use of laboratory and diagnostics opportunities to address all three diseases in more efficient and patient centred manners.

Objectives

The proposed regional workshop aimed at bringing laboratory specialists from the Region together to strengthen TB, HIV and viral hepatitis laboratory diagnostics, testing and monitoring capacity, with the following objectives:

- To gain an overview of ELI's TB related work and activities;
- To update WHO recommendations on TB, HIV and viral hepatitis diagnostics, testing and monitoring strategies;
- To exchange information and knowhow on novel and innovative technologies to be used as an entry point for integrated laboratory services for all three diseases;
- To discuss the role of molecular and genome sequencing based technologies and their benefit for all three diseases;
- Brainstorming on lab diagnostics, testing and monitoring issues relevant and common to TB, HIV and viral hepatitis;
- To reach consensus on priority activities for ELI to focus on.

Expected outputs

- For ELI Core Group members to meet and discuss in person, helping them to work closely as a group;
- For the Core Group to define and agree on at least three priority areas to work on over the next 12-24 months;
- To define the next steps and deadlines for the sub-working group activities for the next 6-12 months.
- To have a comprehensive meeting report.

Welcome and introduction

On behalf of the WHO Regional Office for Europe, Dr Masoud Dara, coordinator for Communicable Diseases and Programme Manager for Joint Tuberculosis, HIV and viral Hepatitis Programme (JTH), welcomed participants to the first face-to-face meeting of the renewed European Laboratory Initiative (ELI) for TB, HIV and viral hepatitis Core Group. Dr Dara welcomed the new members of the group and emphasized the need for integration across all the sectors to end TB, HIV and Malaria. He also referred to the recently launched UN Common Position Paper to end HV, TB and viral Hepatitis in Europe and central Asia through Intersectoral Collaboration. Technologies should not only be state of the art but also be implementable. ELI has a role in supporting and monitoring countries' implementation.

Dr Francis Drobniewski, chairperson for the ELI group and Professor of Global Health and Tuberculosis at Imperial College London, provided participants with an overview of the meeting structure. In line with WHO policy, Declarations of Interest and Confidentiality Undertakings had been completed, signed and returned by all participants, with none of the declared interests deemed to constitute a conflict of interest. Dr Drobniewski reflected on the general success of managing TB and on the remaining challenges to address the transition from drug sensitive to drug resistant forms of TB. Dr Drobniewski emphasized the need to integrate diagnostics, care and laboratory services for TB and HIV; one aspect of this being the role of whole genome sequencing (WGS) as a tool for identifying drug resistance, surveillance and transmission. Dr Drobniewski suggested that ELI should align guidelines and recommendations with WHO documents, as well as working together with the Green Light Committee (GLC) and HIV Treatment Reference Group (HIV-TRG) in areas of overlap.

Summary of presentations and discussions from Day 1

1.1 TB, HIV and viral hepatitis in the WHO European Region

Dr Masoud Dara highlighted the large variation in TB incidence rates in the 53 countries in the WHO European region in terms of rates of TB infections and the requirement to focus on the 18 high priority countries. There has been increasing incidence of MDR-TB as well as TB and HIV co-infection, driven by the increase in HIV in many eastern Europe and central Asian countries. Dr Dara emphasized the importance of early diagnosis to start patients on the right trajectory to receiving timely and effective treatment to reduce rates of transmission. Significant progress is required to reach the 90-90-90 HIV targets in the Eastern Europe and Central Asia (EECA) region, where the average currently stands at 74-50-72. The WHO is working with Ministries of Health (MoH) from 14 EECA countries to scale up diagnosis, combat stigma and adopt the 'treat all' approach. Meanwhile, mortality rates of viral hepatitis exceed HIV and TB combined. This year a ground-breaking commitment was made by the UN to end HIV, TB and viral hepatitis in Europe, the next step is implementing it.

In most countries in the European region, laboratory services for HIV, TB and viral hepatitis are not integrated and operate as vertical programmes. Integration would be desirable in some countries in order to improve diseases management and reduce costs. Integration is possible at three levels: sample collection, diagnostic integration, and care provision. Additionally, new technologies, such as Next-generation sequencing (NGS) might be driving integration in some settings at the technical level, where only one piece of equipment is purchased that has to be shared between the different disease programmes. However, obtaining sequences and interpretation of NGS results may require a high degree of specialization.

1.2 Presentation of ELI's TB related activities and its future vision and ELI's Terms of Reference

Dr Soudeh Ehsani, ELI Core Group Secretariat and Technical Officer for JTH at WHO Regional Office for Europe, provided an overview of ongoing ELI projects, which have focused around meeting targets set out in the Tuberculosis action plan for WHO European Region 2016-2020. ELI activities have been in three major areas of action: developing regional TB diagnostic algorithms; TB laboratory maintenance, biosafety and quality assurance; and recommendations for appropriate use of WHO approved rapid molecular tests for TB and MDR-TB.

The current activities of ELI include:

- Updating laboratory diagnostic algorithms, which were developed as user-friendly documents adapted to the capacity and needs of the regions;
- Development of a Training Tool Kit on use of molecular line probe assays for detection of resistance to second-line TB drugs (SL-LPA) in collaboration with the Global Laboratory Initiative (GLI);
- Development of TB drug susceptibility testing (DST) quality assessment dashboard;
- Ongoing training for engineers and lab technician throughout the region;
- An opinion piece on the integration of TB, HIV and viral hepatitis diagnostic services.

In addition to the three previously mentioned areas of action, ELI will now also focus on integration of TB, HIV and hepatitis diagnosis, testing and monitoring services (Figure 1).

Figure 1: ELI's major focus areas and working groups

The terms of reference of ELI and its core group members under the overall coordination of WHO Regional Office for Europe on TB, HIV and viral Hepatitis diagnostics, testing and monitoring are as follows:

- Adaptation of global WHO guidelines and guidance documents to meet and respond to the needs and capacities of Member States within the WHO European Region;
- Support countries in implementing global and regional WHO policies, guidelines and guidance documents for existing and future diagnostic tests and strategies;
- Develop consensus guidance documents on integrated laboratory services on TB, HIV and viral hepatitis taking a health systems approach into account;
- Contribute to the development of evidence based technical documents;
- Identify needs for TB, HIV and viral hepatitis laboratory strengthening in the Region;
- Provide support on effective transfer and share of novel technologies;

1.3 WHO HIV and viral hepatitis diagnostics, testing and monitoring strategies and recommendations

Dr Lara Vojnov (WebEx), Technical Officer and Diagnostics Advisor at WHO Headquarters, provided an overview of current WHO recommendations for HIV testing: in high prevalence setting (≥5%) use of two consecutive rapid diagnostic tests (RDTs) is recommended for positive diagnosis, in low prevalence settings (<5%) use of three consecutive RDTs is recommended for positive diagnosis; task sharing HIV testing services with lay providers is recognized as an effective way of increasing uptake and reducing costs; testing at the facility level, community level, assisted partner notification and self-testing are all recognized modes of HIV testing. WHO HIV Testing Services guidelines will be updated in 2019.

Most countries in the region are adopting or implementing the WHO policy for Treat All ART initiation among adults and adolescents. There is an adherence problem with patients starting on treatment with advanced HIV disease, accounting for 35-40% of total patients starting on treatment. There is a need for further decentralization of assays to test for CD4, CrAg and TB in patients with advanced HIV disease for use at point of care.

Dr Vojnov outlined some of the issues arising from 2016 WHO ARV guidelines recommendation of viral load testing 6 and 12 months after a patient starts on treatment and then yearly. If two consecutive tests show that viral load is too high, the patient is assumed to be failing and switched to second-line treatment. Dr Vojnov suggested that this algorithm may need revising to prevent patients from being switched to second-line unnecessarily if the problem is adherence. In many low- and middle-income countries (LMICs) it is challenging to transport plasma samples to the laboratory in under 72 hours for testing. Dry blood spot (DBS) testing is currently being considered as an alternative. So far, results have shown that DBS only detects 85% of failing patients, however this may be viable if it enables more patients to be tested. Despite increasing viral load testing, results are not being acted on enough to move patients through algorithms to receive appropriate treatment. Physicians may be hesitant to use viral load testing results, due to long turn-around times for receiving results, inconsistency in results leading to mistrust of results, and reluctance to switch patients to second-line treatment.

Dr Vojnov touched briefly on the Hepatitis B and Hepatitis C testing guidelines. Hepatitis B guidelines recommend use of a rapid diagnostic test (RDT) to detect hepatitis B surface antigen, followed by confirmatory DNA nucleic acid test and further assessment for individuals that test positive, to determine who should move onto treatment. Hepatitis C guidelines recommend HCV antibody assay (either RDT or lab-based immunoassay), followed by confirmatory nucleic acid test. All patients with confirmed HCV infection should be offered treatment, however, further assessment is recommended with selection of an appropriate treatment regimen. More nuanced thinking is required to identify a more appropriate algorithm for hepatitis B.

Dr Vojnov reiterated the need for integration of diagnostic and laboratory services for diseases that use the same molecular techniques. Integration may be facilitated by more advanced technologies that enable decentralization of testing closer to the point of care.

1.4 Role of polyvalent diagnostic tools for TB, HIV and hepatitis

Dr Natalia Shubladze, ELI core group member and Research Consultant at National Centre for Tuberculosis and Lung Diseases in Georgia, drew attention to insufficient testing of HIV-positive patients for TB and inadequate linkages between HIV and TB services in the region. Dr Shubladze highlighted the opportunity for polyvalent diagnostic tools, which can sequentially or simultaneously test for multiple infectious agents, to bridge the gap between disease-specific laboratories resulting

in more efficient and cost-effective systems, increased access for patients, improved management of co-infections, and ultimately better quality of care.

Dr Shubladze referenced the recent WHO publication on Considerations for adoption and use of multi-disease testing devices in integrated laboratory networks (2017) and the key considerations from this document that the ELI group could provide inputs for: selection of a multi-disease device testing product and site of deployment; development of biosafety documents for specimen management; development of standard operating procedures for multi-disease devices; developing training programs for supervision, monitoring, and conducting training; training clinicians on all types of tests available; assisting the development of quality management systems for multi-disease devices; and coming up with a software concept for data management and integration.

The number of multi-disease diagnostic platforms is increasing as the field is rapidly expanding. A recent report by Unitaid[1] analysed 58 devices, including two that can be used for HIV/TB/HCV. As many devices are pending endorsement, WHO generally advise countries to map facilities, sites and patients and choose equipment that is fit for purpose.

1.5 Role and place of Next Generation Sequencing for TB and integrated laboratory services

Dr Matthias Merker, who presented on behalf of Professor Stefan Niemann (ELI core group member), provided an overview of the steps of next generation sequencing (NGS): DNA extraction, DNA fragmentation library preparation, sequencing of fragments to generate millions of reads, and alignment of the sequences against a reference genome, followed by additional bioinformatic interpretation. During data interpretation, mutations that are associated with resistance to certain antibiotics may be found. These data can be used for first-line and some second line DST (i.e. genotypic determination compared to phenotypic microbiological determination), to draw core genome trees, and to carry out surveillance.

When using NGS for DST, the mutational results will have been compared to a minimum inhibitory concentration (MIC) mg/L cut off using a phenotypic microbiological assay to determine whether the strain is susceptible enough to use the drug. In some cases, a higher drug dose can compensate for mutations associated with low-level drug resistance. However, discordances between the genotypic and phenotypic information are possible, which can be difficult for clinicians to interpret.

Dr Merker described some research that he worked on comparing use of phenotypic and molecular DST for MDR-TB therapy. In this research resistance to different antibiotics was deduced based on resistance prediction data from different molecular tests that were carried out on a small cohort of 25 MDR-TB patients admitted to the TB reference centre in Borstel, Germany between 2013 and 2015. Hypothetical MDR-TB regimens were designed based on individual molecular resistance tests that were compared to phenotypic DST results. There was generally high agreement between phenotypic DST and molecular resistance predictions, indicating potential for WGS-based MDR-TB therapy.

Dr Merker finished his presentation by summarising important advantages and disadvantages of using WGS for surveillance and susceptibility testing.

Advantages for surveillance:

[1] UNITAID, Multi-disease diagnostic landscape for integrated management of HIV, HCV, TB and other coinfections. Geneva: UNITAID; 2018 (https://unitaid.eu/assets/multi-disease-diagnostics-landscape-for-integrated-management-of-HIV-HCV-TB-and-other-coinfections-january-2018.pdf)

- High resolution and specificity
- Inferences on direction of transmission
- Differentiation between endogenous and exogenous drug resistance

Challenges for surveillance:

- Determining the variability of the molecular clock across different situations (e.g. drug resistant and susceptible disease, HIV positive and negative patients, across different lineages).
- Assessing the impact of WGS in low and high incidence settings.
- Establishing quality assurance and a standardised nomenclature.

Advantages for susceptibility testing:

- When compared to culture, reduced time and costs.
- When compared to line probe assays/GeneXpert, comprehensive target analysis that predicts susceptibility and resistance.

Challenges for susceptibility testing:

- Characterising the whole 'resistome'
- Linking individual mutations to clinical outcome
- Establishing quality assurance and standardised nomenclature.

1.6 New technologies for testing of drug resistant HIV

Dr Roger Paredes (WebEx), ELI Advisor and Principal Investigator in the Microbial Genomics group at Institut de Recerca de la Sida IrsiCaixa, called attention to the alarming rise in NNRTI resistant strains of HIV in many parts of the world. For the first time, the WHO has issued an algorithm for HIV drug resistance, which advises countries with a level of resistance above 10% to either to switch to dolutegravir (DTG) if it is affordable or consider introducing DST. There are three options for resistance testing: Sanger sequencing, point of care assays, and NGS. Resistance testing technologies are prioritized in terms of price (<50USD), simplicity, technical robustness and ability to inform treatment programs.

Some might think that NGS is far from being adopted; however in reality more than two thirds of WHO-accredited laboratories either have NGS in place or have plans to implement it. The cost of NGS is steadily declining due to technical advances in carrying out library preparation, which is the most expensive stage. For HIV resistance testing, most laboratories that have adopted NGS do not sequence the whole genome but focus on key HIV drug targets.

One of the main limitations of NGS is the huge amount of data that it produces, which so far has to be dealt with using complex bioinformatics. However, if these data are entered into a structured database it can be used for real time surveillance. There are a number of cloud-based pipelines, such as HyDRA, MiCall and PASeq.org, where you can input raw data to produce a resistance report without requiring the user to have any bioinformatic expertise. Above a certain threshold of sensitivity (around 15%) these services perform more or less equally but a lower sensitivity (around 5%) discrepancies start to occur due to different secondary quality control strategies, reference mapping approaches, variant qualification etc. Developers of these pipeline services met in Winnipeg, Canada to agree on a consensus for NGS read quality control and quality assurance, alignments, reference mapping, HIV variant calling, drug resistance interpretation, and data analysis and management. The Winnipeg consensus document was the outcome of these discussions[2] . A

[2] Hezhao Ji, Eric Enns, 3 Chanson J. Brumme, Neil Parkin, Mark Howison, Emma R. Lee, Rupert Capina, Eric Marinier, 3 Santiago Avila-Rios, Paul Sandstrom, Gary Van Domselaar, Richard Harrigan, Roger Paredes, Rami

new unified format for data sharing and analysis was also developed called Amino Acid Variant File (AAVF). This is a powerful tool because it standardises outputs to facilitate cross-country merging and sharing of data sets.

Dr Paredes referenced a recent study published by Pan-African studies to Evaluate Resistance (PASER), investigating how well outcomes could be predicted at different NGS thresholds of sensitivity using MiCall sequencing. The study found that detection of resistance was most effective at a threshold of between 15-20%. At a threshold of 5% increased sensitivity is accompanied with loss in specificity, resulting in false positives. Therefore, a threshold of around 15-20% (similar to Sanger level) is generally advisable.

Following Dr Paredes presentation there was some discussion around the sustainability of these free-to-use cloud-based services. Dr Paredes conceded that long-term economic sustainability of these services, which must be affordable to low-income countries, is a challenge yet to be solved. It is not clear whether they would remain free of charge. Much of the existing capacity and emphasis is surveillance focussed (contributing to clinical guideline development) rather than for immediate individual clinical action.

The issue of data protection and how this would be influenced by the new EU Data Protection Law was also brought up.

1.7 Implementation of WGS: country experience from Kyrgyzstan

Dr Gulmira Kalmambetova, ELI core group member, provided some context on TB in Kyrgyzstan. Although the incidence of TB in Kyrgyzstan has been declining over the past two decades, the proportion of TB patients who have X/MDR-TB infection has been increasing. Furthermore, X/MDR-TB patients have poor treatment outcomes due to lack of timely identification of susceptibility patterns preventing initiation of effective treatment. Dr Kalmambetova expressed her optimism that the introduction of NGS in Kyrgyzstan will enable earlier identification of drug susceptibility patterns compared to phenotypic microbiological based assays facilitating individualized therapy and improve treatment outcomes.

Stop Transmission of TB in Hospitals (STTH) is a capacity building project with an operational research component, funded by USAID. The project aims to implement Defeat-TB infection control policies and to build epidemiological and laboratory capacities in the National Reference Laboratory to monitor and evaluate the impact the infection control policies are having in reducing TB transmission. One element of STTH project is implementation of WGS at national laboratories.

The challenges that Kyrgyzstan experienced when implementing WGS included training for lab staff, which was provided in English and needs to be standardized; ensuring that training for clinicians is based on latest information and is regularly updated; developing standard lists for equipment, reagents and consumables; developing an operation practice list; maintaining equipment and databases; bioinformatic interpretation of NGS data; and registration of items in the country and customs clearance.

Future plans:

- Evaluate cost-effectiveness of WGS;

Kantor, Marc Noguera-Julian. Bioinformatic data processing pipelines in support of next-generation sequencing-based HIV drug resistance testing: the Winnipeg Consensus. J Int AIDS Soc. 2018 Oct; 21(10): e25193. Published online 2018 Oct 22. doi: 10.1002/jia2.25193.
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6198166/

- Optimize TB diagnostics with respect to the latest WHO recommendations;
- Establish regular transportation of specimens between primary health clinics, TB hospitals and TB lab networks;
- Use WGS for all MDR-TB isolates from STTH project and ensure sustainability of that technology.

1.8 UK's experience of using WGS for MDR-TB diagnosis

Dr Drobniewski emphasized that although WGS is a useful tool it is important to consider the practicalities of using this technique on a routine basis. Dr Drobniewski described a research project that he had led, investigating evolution and transmission of MDR-TB using WGS in a Russian population[3]. This work suggested that use of WGS on a routine basis for DST of TB cases may be feasible.

Following on from the above-mentioned population study in Russia, a retrospective analysis was conducted in the UK which found good concordance between genotypic and phenotypic analyses of microbiological cultures for TB identification and first line drugs. Subsequently, at a few pilot centres in the UK, WGS was run side by side with existing molecular-based and microbiological methods that were currently being used, to compare cost and performance. Both services were found to perform more or less equally in terms of sensitivity and specificity. The economic analysis was very approximate; however the findings suggested that WGS was slightly cheaper. Based on these results, diagnostic reference services using WGS were introduced in the UK. It was important to realize that the UK was already applying VNTR 24 loci analysis to all TB cultures so that an existing budget could be transferred to WGS.
From receipt of the mycobacterial culture to the report being sent out, takes around 7-10 working days, which increases the turn-around-time for diagnosis of TB but reduces the turn-around-time for identification and DST for patients with MDR-TB using microbiological methods.

The ultimate goal is to perform WGS directly using clinical samples to deliver faster results (ideally at the point of care). Several studies have investigated different ways of performing WGS on patient sputum, but so far most attempts have either not achieved sufficient depth and coverage or have been too expensive and time consuming. Targeted sequencing of key resistance genes direct form patient specimens looks a promising alternative to WGS. Prof Drobniewski expressed his optimism that performing WGS on clinical samples would become a possibility in the future (and was essential if WGS or targeted sequencing was to be truly clinically useful).

1.9 Panel discussion on WGS use for TB, HIV and viral hepatitis

During the panel discussion between Prof Francis Drobniewski, Dr Matthias Merker, Dr Roger Paredes, Dr Claudio Köser, Dr Gulmira Kalmambetova, Dr Rob Schuurman (via WebEx) and Dr Soudeh Ehsani, the following topics were discussed:

Use of different approaches for different diseases. Several group members expressed that line probe assays are inadequate for resistance-testing when there is a high level of genetic variation, for example in HIV. There are fewer technological approaches available for performing WGS for HCV as this represents less of a commercial interest to businesses. It may be appropriate to use different technology to test different disease, and then consider how the technology could be integrated.

[3] Casali, N., Nikolayevskyy, V., Balabanova, Y., Harris, S., Ignatyeva, O., Kontsevaya, I., Corander, J., Bryant, J., Parkhill, J., Nejentsev, S., Horstmann, R., Brown, T. and Drobniewski, F. (2014). Evolution and transmission of drug-resistant tuberculosis in a Russian population. *Nature Genetics*, 46(3), pp.279-286.

The need to consider what the tests are being used for. For HIV, it was agreed that a targeted approach is more than enough for testing in clinics (and would permit ongoing use of earlier Sanger sequencing-derived data). A targeted approach for TB identification and DST may also be an alternative to WGS and can be performed directly on patient specimens. If WGS is used, there is the issue of sensitivity. However, WGS can be useful for generating data for global surveillance. In this case, if a country does not have the capabilities to carry out WGS, samples can be transported to external specialised reference laboratories.

The need to consider the country context. In countries where not all genome information is used, WGS is not justified due to additional cost and significant delay. In countries where contact tracing is used, then WGS is justified. Resistance testing is not always necessary depending on the level of resistance and the drugs available. In Botswana, where DTG is available, resistance testing is not necessary because if a patient is failing, they can just be switched to DTG.

Challenges implementing WGS. Some participants brought forward some of the major barriers to implementing WGS. One of these was the complexity of performing WGS in laboratories compared to Sanger sequencing. Another issue was insufficient human resources to carry out WGS, as most funding is channelled to carrying out ELISA and viral load testing. Another challenge raised were the strict regulations for medical devices and reagents entering countries.

1.10 Round table discussion: Laboratory diagnostics, testing and monitoring issues relevant and common to TB, HIV and hepatitis

A round table discussion between participants was led by Prof Francis Drobniewski. The main topics that were discussed are summarized below.

Maximise use of equipment. Vertical programs often purchase the wrong quantity of devices. Equipment in some disease programs does not get used to its full capacity, while other programs do not have enough equipment. If it is multi-disease capable equipment, it makes sense for it to be used by other disease programmes to get full use of the equipment. It may be necessary to prioritize what samples need to be run on given equipment so that the instrument is not overrun with samples from one disease program.

Transportation of samples. Transportation of samples from primary care clinics to the different disease laboratories is inefficient in many settings. There are biosafety, logistical, legal issues when transporting clinical samples; for example needing to keep the samples contained and cool as well as protection of patient data. In Georgia, postal workers have been trained to handle infected fluids and the provision and use of cool boxes. Integration of vertical disease programmes should reduce the amount of sample transportation as any one laboratory can test for multiple diseases.

Incentives for integration. In some cases, monetary incentives have been used successfully to overcome laboratory staff's reluctance to take on workload from other disease programs. However, as the Global Fund is retreating from most countries, this would have to be funded domestically. In some settings, other intrinsic incentives have proven to be effective.

Further training for staff. It may be most efficient to have one team that processes all samples on one piece of equipment, for example GeneXpert. If laboratory staff are expected to run clinical samples for other disease programs, they will need to receive further training. However it was argued that this was entirely feasible.

Overcome biosafety issues. Laboratory staff may be reluctant to handle clinical samples that they are not used to working with. In most cases, these samples would be capped so biosafety issues are minimal, but some training may still be required.

Tackle job insecurity concerns. If integration does not occur across the whole system at the same time, this may result in too much workload in some departments and not enough in others. This could lead to job insecurity. Furthermore, directors of specialised disease laboratories may be reluctant to integrate diagnostic activity for fear of job loss. There is a need to ensure that integration occurs in a coordinated and synchronized manner to limit potential or actual job losses.

Generating political will for integration. Integration is generally a political conversation. However, professional lobbies have a lot of political power and may undermine the process of integration if there is fear of people losing their jobs. There is need to map out where equipment is and how much it is being used to ensure maximum utilisation of equipment and to even out the workload.

Presentations and discussions from Day 2

2.1 ELI algorithms update based on the new MDR/RR-TB treatment regimen

Dr Ehsani provided a brief background of the ELI algorithms, which were developed for the initial diagnostics of all presumptive TB cases and for follow up of patients with drug sensitive TB and patients with MDR-TB. The current ELI TB algorithm initially prescribes molecular based testing to test for the presence of TB strains. For patients with presumptive MDR-TB, the pathogen is detected by molecular diagnostics and culture-based phenotypic DST. Further microbiological DST and SL-LPA are used to identify the drug susceptibility pattern of the pathogen to develop an individualized regimen for the patient.

To meet the demands related to new MDR-TB treatment recommendations (final recommendations will be released in December 2018; there has been an initial WHO advisory), there is a need to update the ELI TB diagnostic laboratory algorithms. One aspect of this is scaling up DST, prioritizing drugs in Group A and B: levofloxacin/moxifloxacin, bedaquiline and linozolid; clofazamine (there is no standardised DST method for cycloserine). In addition to the presently recommended LPA testing for SLID and FQ, the algorithms should be extended to include indirect DST of bedaquiline and linezolid in the liquid culture based MGIT assay. The updated WHO recommended critical drug concentrations for *M. tuberculosis* DST should be used. Where previously culture was suggested for first-line LPA (FL-LPA) that showed resistance to isoniazid, use of SL-LPA is now suggested for isoniazid mono-resistant cases (as well as culture based DST). The new guidelines no longer recommend the use of kanamycin and capreomycin, which should be replaced with amikacin where needed. Anticipating that countries will not be able to adapt treatment regimens to the new guidelines immediately, ELI recommends that laboratories continue reporting results for kanamycin and capreomycin, which can be disregarded by clinicians if they do not need to use these drugs (or are using amikacin instead).

During the discussion, the difficulty procuring and legally importing enough bedaquiline for research and treatment purposes was raised. A strategy was suggested whereby labs perform DST for bedaquiline first to find out if it worth trying to procure on a larger scale for treatment (where there were importation obstacles). Supplies of pure drug powder for bedaquiline (and delamanid) are being made available by the manufacturers.
These issues will be discussed further at the next TB Green Light Committee (GLC) meeting. For example, although the importance of cycloserine for MDR-TB treatment is emphasised in the latest guidelines, there is no current DST method for cycloserine recommended by WHO. However, in some settings clinicians are still insisting that labs report on DST for this drug. This is particularly a

problem in ex-Soviet countries, where clinicians drive laboratory activity. Laboratories should make it clear that they cannot reliably report on this drug and a wrong result may lead to the wrong treatment choices for the patient.

2.2 Updates from the UNION meeting on SL-LPA result interpretation and implications for the SL-LPA training toolkit

Dr Claudio Köser, ELI group member and Visiting Scientist at the University of Cambridge, provided some background on the WHO endorsement of the Hain line probe assays (LPA), and, how since these endorsements, there have been changes to how resistance is defined phenotypically and genotypically. In response of these changes, WHO released a Critical Concentration report for second-line drugs[4], DST manual[5], and NGS guide[6]. GLI also released an LPA report[7] to align the interpretation of both Hain assays with the changes to the critical concentrations.

When interpreting the results of the LPAs, resistance is reported if either a mutant probe binds, or a wild type probe does not bind, assuming that all mutations in this region would cause resistance. However, even in monomorphic organisms it is possible to have mutations that do not correlate with resistance, leading to systematic false positive results. Normally, if a wild-type probe does not bind (even if the corresponding mutant probe did not bind) resistance is assumed because it is globally rare to have a non-resistance conferring mutation. However, strains that harbour mutations that cause systematic false-resistant results have been shown to be frequent in some setting, which significantly affects the positive predictive value of the LPAs. From now on, if a mutant probe develops this will be reported as 'resistance detected', whereas if only a wild type probe does not develop this will be reported as 'resistance inferred' to capture the possibility of systematic false resistance.

Dr Köser outlined some of the inconsistencies in the aforementioned GLI document for the interpretation of LPA results. First, there was insufficient evidence to show that some of the probes cover valid resistance makers. Second, 'likely' was used inconsistently as a reporting term and may cause confusion amongst clinicians. Third, there are inconsistencies between the NGS guide, GLI guide and DST manual regarding the classification of resistance mutations. There is a need for a consensus document to address these points.

The epidemiological cut off value (ECOFF) corresponds to the highest concentration/upper end of the phenotypically wild-type (pWT) MIC distribution. Strains with MICs > ECOFF are referred to as phenotypically non-wild type (pNWT). Clinical breakpoints (CB) distinguish organisms that are likely to succeed on therapy from those that are likely to fail. CBs are set using pharmacokinetic, pharmacodynamics and clinical data. CBs define susceptible (S), susceptible at increased exposure

[4]World Health Organization.(2018) Technical report on critical concentrations for TB drug susceptibility testing of medecines used in the treatment of drug-resistant TB. Geneva: World Health Organization (http://www.who.int/tb/publications/2018/WHO_technical_report_concentrations_TB_drug_susceptibility/en/)

[5]World Health Organization, Technical manual for drug susceptibility testing of medicines used in the treatment of tuberculosis. Geneva: World Health Organization; 2018 (http://www.who.int/tb/publications/2018/WHO_technical_drug_susceptibility_testing/en/)

[6] World Health Organization. (2018). The use of next-generation sequencing technologies for the detection of mutations associated with drug resistance in Mycobacterium tuberculosis complex: technical guide. World Health Organization. http://www.who.int/iris/handle/10665/274443.

[7] Global Laboratory Initiative (2018). Line probe assays for drug-resistant tuberculosis detection- Interpretation and reporting guide for laboratory staff and clinicians. (http://www.stoptb.org/wg/gli/assets/documents/LPA_test_web_ready.pdf)

(I), and resistant (R) categories. Six different S/I/R classifications are possible, depending on the value(s) of the CB(s) relative to the ECOFF.
The MIC distributions for susceptible, low-level resistance and high-level resistance for moxifloxacin overlap to some degree resulting in 'areas of technical uncertainty' (i.e. if an MIC falls into this area, the strains cannot be classified unequivocally). If a high-level mutation is detected, the drug should not be used under any circumstance (and arguably no further phenotypic DST is required). If only a low-level resistance is detected, there is a risk that the strain in question is actually high-level resistant because of mutation missed by the genotypic assay, which has to be investigated using phenotypic DST at the CB.

Dr Köser concluding by asserting the need to clarify inconsistencies (e.g. when phenotypic testing is an appropriate confirmatory test and how to handle discordant results). Currently, the GLI guide recommends reporting the genotypic results as a mixture of probes and mutations, but it was suggested that either only probes, only mutations or only the clinical interpretation should be reported to avoid confusion. However, labs should electronically store binding patterns to enable for systematic errors to be readily identified. Dr Köser expressed the need for prevalence specific algorithms to allow clinicians to make the most appropriate clinical decision for 'resistance inferred' cases.

2.3 Group Discussions on the SL-LPA updates

- When reporting results of wild-type and mutant probes, if there is any risk of resistance (i.e. 'resistance inferred') clinicians should be advised to act as though it is resistant until proven otherwise, to avoid major errors.
- Labs should be encouraged to electronically record results and monitor frequencies so that they can identify if there is a local clone with a non-resistance inferring mutation.
- Consensus document should be user-friendly, practical, and relevant to the region and provides clarification on inconsistencies and clear-cut interpretations based on best evidence.
- As the document would be a WHO document, DST and NGS documents should be used as guidelines and GLI document can be used for guidance.
- A part on HIV will need to be added.
- The SL-LPA training tool should be published first, followed by an interpretation manual.

2.4 Group Discussions on algorithm update

- The algorithm update should be user-friendly, adapted to the needs and capacity of region;
- Figures in the algorithm need to be updated;
- Needs to include integration of HIV and TB.;
- Correct data interpretation and reporting (including discordant results);
- Specific updates:
    - Scale up for DST, prioritizing levofloxacin/moxifloxacin, bedaquiline and linozolid;
    - Indirect DST of bedaquiline and linezolid in the liquid culture based MGIT assay;
    - No longer recommend use of kanamycin and capreomycin (replacement with amikacin if needed;
    - Use of SL-LPA for isoniazid mono-resistant cases.

2.5 DST quality assurance dashboard

Dr Shubladze gave a description of the DST quality assurance dashboard that she is developing, a tool primarily developed for an external assessor to identify the reasons for low DST use and the delay of DST results. The tool assesses how the recommended algorithm is implemented, the type of samples collected, how Xpert MTB/RIF diagnostics is performed, how FL- and SL-LPA diagnostics is

performed, how solid DST is performed (media preparation, equipment), how liquid DST is performed, whether/how results are compared, performance indicators for each test and turn-around-time (TAT). The tool is structured as a checklist with questions. Questions have individual weights; fulfilling more important questions adds more to the final score. Answers can be scored complexly i.e. not only yes and no (1.0/0.0) but also partial answers (0.2,0.5 etc). Results for every section are calculated automatically to create scores for overall progress.

The tool will be first produced in Russian based on the countries it is initially intended to be used by, but later translated into other languages to allow localization. The tool can work on many platforms, including mobile and touch screen devices. Dr Shubladze welcomed suggestions from the group.

Some suggestions from the group included outsourcing creation of the questionnaire to a sociologist or professional who has expertise in developing questionnaires, use of cross-checking questions, piloting its use to ensure clear understanding of questions and printable checklists and conclusions that can be displayed in the lab.

2.6 Biosafety cabinet maintenance training

Dr Rasim Tahirli, Laboratory Head of the Tuberculosis Training Centre in Azerbaijan and ELI Core Group member, recounted Azerbaijan's experience of trying to get certification of biosafety cabinets (BSC). Many BSCs were in a state of disrepair, with damaged gaskets, leaking areas and filters that needed replacing, but paying for a certifier was very expensive. In 2012, the government decided to recruit an engineer, who would undergo a training course in the private sector to be able to replace the filter, perform a leakage test, particle counting of HEPA-Filters, pressure measurement, smoke detection test, and measurement of airflow velocity at the entrance of the BSC. The training of the engineer was partly funded by a budget from Expand-TB to implement certification. Subsequently, the WHO Regional Office for Europe organized a Sub regional training on tuberculosis laboratory biosafety cabinet maintenance in 2017 and a Mentoring Mission for engineers in 2018 to improve regional and national BSC maintenance. These training courses have enabled engineers to carry out certification of BSC independently.

2.7 TB Laboratory biosafety-infection control tool (TB-ICA tool)

Dr Sergejs Nikisins, WHO laboratory and IPC consultant and ELI Adviser, updated the group on the TB-ICA tool that he is developing. The intended use of the tool is to assist with infection control assessments in TB laboratories, inpatient and outpatient departments. The tool is primarily designed for use by laboratory and health professionals but has been designed to yield reliable results when used by a non-specialist.

The tool assesses the risk of TB either infecting the individual or being released into the environment. The tool is built on an excel spreadsheet that contains questions and sub-questions around the core elements of infection prevention and control (IPC), including: administrative control, environmental control and Personal protective equipment (PPE). Level of Biorisk is determined by combining the probability of exposure with the severity of the consequences of possible exposure.

Prior to the introduction of the tool to the end user, training and tool mentoring will be provided to the facilities. There will be a user-manual on how to use the tool provided together with the tool in form of a written SOP or/and in a format of Video instructions. The lab part of the TB ICA tool could be piloted late autumn 2018 in Georgia upon which potential remaining gaps and improvements will be considered.

Roundtable discussion: ELI Future directions

- More studies on cycloserine required to define ECOFF and critical concentration.
- Discuss potential connectivity solutions to improve reporting of test results, epidemiological surveillance. This topic has been raised at several recent global conferences and no ideal solution has been found. Many commercial connectivity solutions are built around one method (i.e. GeneXpert) and do not provide comprehensive solution for other methods. There are also issues with data privacy. This should be discussed at future meetings.
- Inclusion of latent TB in future discussions. More cost-effective to ensure that people with latent TB are also being treated.
- If WGS becomes a routine procedure for DST in clinical laboratories, clinicians need to be taught how to handle uncertain results, as many clinicians are used to thinking in terms of a patient either being infected with a susceptible or resistant strain only.
- Need to develop rules around data sharing, how long information should be stored for and who owns the data.
- Need to discuss WGS not as test, but more as a dynamic system. As technology and understanding is constantly changing, retrospective sequencing data is revisited and reinterpreted.
- Countries with a high prevalence of TB have a lot of strains to analyse but not enough capacity. Countries with a low prevalence have many experts but not enough strains. Opportunity for sharing expertise and samples between countries.

List of proposed actions and implementation

- **Expert opinion piece on integration of TB, HIV and viral hepatitis**
- **Algorithm for TB and HIV diagnosis and treatment updated**
- **Technical document on the integrated use of GeneXpert for TB, HIV and viral hepatitis**
- **DST quality assessment dashboard**
- **Consensus paper on pros and cons of Next Generation Sequencing for all three diseases TB, HIV and viral hepatitis**
- **WHO global guidelines on Latent Infection adapted to Euro as part of the WHO Euro policy guidance document**
- **SL-LPA online training toolkit, ELI SL-LPA interpretation manual**

Closing comments and next steps

Professor Drobniewski summarised the main agreed next steps which were loosely arranged around two themes, (1) the need for greater integration of TB, HIV and hepatitis diagnostic services (Expert opinion piece; Updated Algorithm for TB and HIV diagnosis and treatment; Integrated use of GeneXpert document as an example for TB, HIV and viral hepatitis integration; Pros and cons of WGS) and (2) the ELI contribution to supporting the new WHO MDRTB guidelines (Update SL-LPA interpretive document, Updated SL-LPA Training manual, DST Dashboard, Biosafety-Maintenance training, Pros and cons of WGS). The ELI would also contribute to a WHO Euro policy guidance document on latent TB infection**.**

Dr Dara thanked the ELI Core Group members for all their voluntary efforts and valuable contributions. Although the group succeeded at bringing HIV on the agenda, more effort is needed to include hepatitis. To ensure that the perspective of all diseases is being covered, it may be necessary to create sub groups that can collaborate, for example there is a need for a consensus document on how to increase HIV and hepatitis C joint testing. Dr Dara encouraged the group to be rational in planning: not over-planning leaves room to be innovative and open to new ideas and technologies. Dr Dara noted the possibility to change position members, for example election of a new chair or appointment of a co-chair. It was agreed that there should be regular teleconferences within the group every three months, especially for completing the proposed actions, which was agreed by the group. Dr Dara closed the meeting.

Annex 1: List of participants

ELI Core Group members

Dr Ana Avellón Calvo*, National Center of Microbiology ISCIII), Spain*
Dr Zamira Baydulloeva*, Project HOPE, Tajikistan*
Dr Vladimir Chulanov, *Institute of Epidemiology, Russian Federation*
Dr Daniela Maria Cirillo, *Emerging Bacterial Pathogens Unit, Italy*
Dr Francis Drobniewski (Chair), *Imperial College London, United Kingdom*
Dr Irina G Felker, *Novosibirsk TB Research Institute, Russian Federation*
Dr Gulmira I Kalamambetova, *National Reference Laboratory, Kyrgyzstan*
Dr Claudio Köser, *University of Cambridge, United Kingdom*
Dr Hasmik Margaryan, *National TB Control Centre, Armenia*
Dr Florian Maurer, *National Reference Laboratory for Mycobacteria, Germany*
Dr Elina V Sevastyanova, *Central TB Research Institute, Russian Federation*
Dr Matthias Merker*, National Reference Laboratory for Mycobacteria, Germany*
Mrs Ecaterina Noroc, HIV Laboratory Coordinator at National AIDS Programme, Dermatology and Communicable Diseases Hospital, Chisinau, Republic of Moldova
Dr Rob Schuurman, *University Medical Center Utrecht, Netherlands*
Dr Natalia Shubladze, *National Centre for TB and Lung Diseases of Georgia, Georgia*
Mr Daniel Simões, EPI Unit - Institute of Public Health of the University of Porto, Member of the Board of Directors, GAT, Portugal
Dr Alena Skrahina, *Republican Research and Practical Centre for Pulmonology and Tuberculosis, Belarus*
Dr Rasim Tahirli, *WHO Collaborating Centre on Prevention and Control of Tuberculosis in the Penitentiary System*, *Azerbaijan*

ELI Advisers

Dr Dimitry Kireev, *Central Research Institute of Epidemiology, Russian Federation*
Dr Sergejs Nikisins, *East University Hospital Laboratory Medicine Center, Latvia (via Webex)*
Dr Roger Paredes, *Institut de Recerca del Sida IrsaCaixa, Spain*

Observers

Dr Maia Alkhazashvili, Manager of Lugar Center, National Center for Disease Control and Public Health (NCDC), Georgia
Dr Meerbubu Sydykova, Laboratory Doctor, National Center of Phtisiology, Kyrgyzstan
Dr Annemarie Wensing, Assistant Professor – medical, University Medical Center Utrecht, Netherlands (via Webex)

World Health Organization

Consultants

Ms Léa Clapier, Consultant, Joint Tuberculosis, HIV and Hepatitis Programme, WHO Regional Office for Europe
Dr Giorgi Kuchukhidze, Consultant, Joint Tuberculosis, HIV and Hepatitis Programme, WHO Regional Office for Europe

WHO Regional Office for Europe

Dr Andrei Dadu, Medical Officer, Joint Tuberculosis, HIV and viral Hepatitis Programme, WHO Regional Office for Europe
Dr Masoud Dara, Coordinator, Communicable Diseases and Programme Manager, Joint Tuberculosis, HIV and viral Hepatitis Programme, WHO Regional Office for Europe
Dr Soudeh Ehsani, Technical Officer Joint Tuberculosis, HIV and viral Hepatitis Programme, WHO Regional Office for Europe
Dr Ogtay Gozalov, Medical Officer, Joint Tuberculosis, HIV and viral Hepatitis Programme, WHO Regional Office for Europe
Dr Sayohat Hasanova, Technical Officer Joint Tuberculosis, HIV and viral Hepatitis Programme, WHO Regional Office for Europe
Dr Antons Mozalevskis, Medical Officer, Joint Tuberculosis, HIV and viral Hepatitis Programme, WHO Regional Office for Europe (via Webex)
Ms Annemarie Stengaard, Epidemiologist, Joint Tuberculosis, HIV and viral Hepatitis Programme, WHO Regional Office for Europe
Dr Martin van den Boom, Technical Officer, Joint Tuberculosis, HIV and viral Hepatitis Programme, WHO Regional Office for Europe
Dr Elena Vovc, Technical Officer, Joint Tuberculosis, HIV and viral Hepatitis Programme, WHO Regional Office for Europe

WHO Headquarters

Ms Lice Gonzalez Angulo, Technical Officer, Laboratories, Diagnostics and Drug-Resistance (via Webex)
Dr Carl-Michael Nathanson, Technical Officer, Global TB Programme (via Webex)
Dr Lara Vojnov, Technical Officer (Diagnostic Advisor), Treatment and Care (via Webex)

Rapporteur

Ms Mia Harley

Annex 2: Meeting agenda

Day 1

Time	Topic	
08:30–09:00	Registration	
09:00–09:15	Welcome and Introduction	**Dr Masoud Dara**, Coordinator, Communicable Diseases, Tuberculosis, HIV and Hepatitis Programme Manager, Division of Health Emergencies & Communicable Diseases, WHO Regional Office for Europe
09:15–09:30	Declaration of Interests	
09:30–09:45	Overview of the meeting agenda	**Prof Francis Drobniewski**, ELI Core Group Chairman, Professor of Global Health and Tuberculosis, Imperial College London
09:45–10:00	TB, HIV and viral Hepatitis in the WHO European Region	**Dr Masoud Dara**
10:00–10:15	Presentation of ELI's TB related activities, its future vision and ELI's ToR	**Dr Soudeh Ehsani**, ELI Core Group Secretariat, Technical Officer, Joint Tuberculosis, HIV/AIDS and Hepatitis Programme, WHO Regional Office for Europe
10:15–10:45	WHO HIV and viral hepatitis diagnostics, testing and monitoring strategies and recommendations	**Dr Lara Vojnov (via WebEx),** WHO Headquarters, Technical Officer, Diagnostics Advisor
10:45–11:15	Coffee break	
11:15–11:30	Role of polyvalent diagnostic tools for TB, HIV and hepatitis	**Dr Natalia Shubladze,** ELI core group member
11:30–11:45	Role and place of Next Generation Sequencing (NGS) for TB and integrated laboratory services	**Dr Matthias Merker** Representing Prof Stefan Niemann (ELI core group member)
11:45–12:00	New technologies for testing of DR HIV	**Dr Roger Paredes** ELI advisor
12:00–12:15	Implementation of WGS: country experience from KGZ	**Dr Gulmira Kalmambetova** ELI Core Group Member
12:15–12:30	UK's experience on using WGS for MDR-TB diagnosis	**Prof Francis Drobniewski** ELI Core Group Chair
12:30–13:00	Panel discussion on WGS use for TB, HIV and viral hepatitis	**Prof Francis Drobniewski, Dr Matthias Merker, Dr Roger Paredes, Dr Claudio Koeser, Dr Gulmira Kalmambetova, Dr Soudeh Ehsani**

13:00–14:00	Lunch	
14:00–15:30	Laboratory diagnostics, testing and monitoring issues relevant and common to TB, HIV and Hepatitis	**Round table discussion led by the ELI chairman**
15:30–16:00	Coffee break	
16:00–17:30	Roundtable discussion: Priority areas for ELI to focus on	**Group discussion led by the ELI chairman**
17:30–18:00	Conclusions day 1	**Prof Francis Drobniewski** **Dr Masoud Dara**
18:00–20:00	Reception and Dinner	

Day 2

Time	Topic	
09:00–09:15	Summary of the previous day	**Prof Francis Drobniewski**
09:15–09:30	ELI algorithms update based on the new MDR/RR-TB treatment regimen	**Dr Soudeh Ehsani**
09:30–10:00	Updates from the UNION meeting on SL-LPA result interpretation and implications for the SL-LPA training toolkit	**Dr Claudio Koeser,** ELI Core Group member
10:00–11:00	Group discussion on the algorithm updates	**TB-ELI core group members**
11:00–11:30	Coffee break	
11:30–13:00	Group discussion on the SL-LPA updates	**TB-ELI core group members**
13:00–14:00	Lunch	
14:00–14:30	DST quality assurance dashboard	**Dr Natalia Shubladze**
14:30–14:45	Biosafety cabinet maintenance training	**Dr Rasim Tahirli** (ELI Core Group Member) **Dr Sergejs Nikisins** (ELI Core Group Advisor via WebEx)
14:45–15:00	TB Laboratory biosafety-infection control tool (TB-ICA tool)	**Dr Sergejs Nikisins**
15:00–15:30	Coffee break	
15:30–17:00	Roundtable discussion: Future directions	**TB-ELI Core Group Members**
17:00–17:30	Closing remarks	**Prof Francis Drobniewski** **Dr Masoud Dara**