UNSGM Designated Laboratories Workshop Report

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The sixth UNSGM Designated Laboratories Workshop took place from 16 – 17 September 2021 in a virtual format.

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Executive summary

This report presents the outcomes of the sixth Swiss UNSGM Designated Laboratories Workshop organised by Spiez Laboratory on a network of trusted laboratories designated under the United Nations Secretary-General's Mechanism (UNSGM) to investigate allegations of the use of chemical, biological and toxin weapons. The initiative links to the Secretary-General's Disarmament Agenda, which asks for adequate preparations to respond to any credible allegation of use of biological weapons.

The workshop took place under conditions imposed by the on-going COVID-19 pandemic and was held in a virtual format. Given the constraints of a virtual format, the agenda was more condensed than at previous workshops. At the same time, this format allowed for a significantly broader participation, both in terms of numbers of participants and geographical representation.

Since the UNSGM depends heavily on what Member States invest into its key components, and recognising the important role of analytical laboratories nominated by Member States, a central issue from the very beginning of the Swiss workshop series has been the establishment of a functional, robust and trusted network of UNSGM designated laboratories. Early on, these discussions confirmed the necessity to develop a collaborative network that would provide transparency and confidence in scientific competencies, analytical skills as well as quality assurance systems, in order to enhance the operational capacity and capability of the UNSGM.

Over the years, the workshop series has served as a valuable platform for sharing information, consulting concepts and ideas as well as planning and synchronising the growing number of practical activities. The latter is particularly relevant when considering the issue of inter-laboratory calibrations, as described in the UNSGM Guidelines and Procedures,[1] where a number of relevant activities at laboratory level are now regularly taking place, including dedicated confidence building and quality assurance exercises. Thus, conceptual discussions have been gradually amplified with practical work that comes with clear benefits for participating laboratories. Not only does regular participation of laboratories in these activities enhance the operational capacity and capability of the UNSGM, it furthermore creates opportunities for self-assessment, benchmarking and improvement. Laboratories gain confidence, and collaborations between them facilitate access to critical assets, such as databases, reference materials, analytical methods and expertise.

This sixth UNSGM Designated Laboratories Workshop had a renewed look at laboratory exercises, topics at the interface with laboratories, laboratory reporting as well as sampling guidance and sample transfer. Key issues of a general nature that will require substantive efforts are the importance of increasing the geographical distribution of laboratories participating in these activities and the need to secure sustainable funding.

The project RefBio that started in 2017 – 'Germany's contribution to strengthening the Reference Laboratories capacity of the UNSGM' – has recently been extended for another three years until 2024. The Robert Koch-Institute leads the project and helps participating laboratories evaluate their capabilities based on their performance in External Quality Assurance Exercises. Ten exercises have been conducted so far and corresponding annual workshops have greatly facilitated the exchange of best practice between participants. Since its inception, par-

[1] Guidelines and Procedures for the timely and efficient investigation of reports for the possible use of chemical and bacteriological (biological) or toxin weapons. https://www.un.org/ga/search/view_doc.asp?symbol=A/44/561

ticipation of laboratories from different regions of the world has gradually increased, but efforts are still needed to generate more significant engagement within the project, particularly from South America, Africa, the Middle East and parts of Asia.

The 2020 exercise was designed in response to the COVID-19 pandemic and addressed laboratory diagnostics of SARS-CoV-2 and other coronaviruses. Participating laboratories rated the exercise as successful and of high interest to them. For 2021, there are three exercises planned in autumn that will address relevant bacteria (Brucella species), viruses (unknown haemorrhagic fever virus), and a toxin (botulinum neurotoxin). Future work under the project RefBio will also significantly invest in the provision of training to laboratories nominated to the UNSGM roster and the setup of a curated reference genome database for use in forensic profiling of bacteria.

The State Key Laboratory of Infectious Disease Prevention and Control (SKLID) of the China Centre for Disease Control (China CDC) announced a new initiative. The planned sand-table laboratory exercise aims at identifying a currently unknown pathogen, which has previously not been described and is presumed to be the causative agent of a potential international epidemic (Disease X), and investigating its animal origin. The exercise is planned to take place in spring 2022 and the United Nations Office for Disarmament Affairs (UNODA) will coordinate participation in the exercise.

Building on the experience gained from previous activities, the Robert Koch-Institute, the Danish Technical University and the Swedish Defence Research Agency (FOI) will start shortly with a new two-year project of dry-lab exercises funded by the US Department of State. The focus will lie on the detection, identification and characterisation of viral pathogens as biological weapons using DNA sequencing data. The two announced exercises are planned to take place in autumn 2021 and spring 2022, respectively.

In terms of interfaces with laboratories, workshop participants learned about the current status of the capstone exercise, offered by Germany and implemented by the Robert Koch-Institute. The first activity already took place in November 2020, with a five-day virtual table-top exercise of the pre-deployment activities of a simulated UNSGM investigation. A number of lessons were learned in the table-top exercise that will help assist in the preparation of the full-scale field exercise that is currently planned to take place in spring 2022. To simulate the complexity of a UNSGM mission, it will involve all relevant stakeholders, including designated laboratories. It is expected that the outcomes will help identify gaps that need to be addressed in the future.

In an attempt to further align the work in support of the UNSGM with the efforts of the OPCW to develop its capacity in toxin analysis, workshop participants received a background briefing on the newly formed Temporary Working Group of the OPCW Scientific Advisory Board on the analysis of biotoxins. It became evident that the outcomes of the Temporary Working Group will be of high relevance to the designated laboratories of the UNSGM and that future exchanges would be of equal benefit to both communities.

Previous workshops have already highlighted the central significance of laboratory reporting, which has prompted recent efforts to develop guidance and templates. Since reporting practices of forensic laboratories are well established, these could be leveraged to guide the development of UNSGM forensic reporting. Forensic laboratory reports contain the information required to support the investigation based on the specific mandate of the investigation team. Within the RefBio project the further development of a template will be pursued in 2022 with additional support from an advisory group.

Flowing from earlier workshop editions, a small working group of experts, led by Canada, has been looking at the interaction of field investigation teams and designated laboratories, particularly with regard to sampling. Recent work includes an outline of needs, a review of existing protocols and

drafting of recommended operating procedures as well as associated guidance documents for environmental biological sampling and for the preparation of biological samples for international shipment.

The final topic addressed the transfer of samples, an issue that has emerged in recent discussions. A virtual table-top exercise is being prepared and coordinated by the US Department of State. This exercise will explore political, legal, regulatory, and technical challenges that could be encountered when moving a biological sample across international borders, and discuss potential solutions. The exercise is planned for the end of 2021 or early 2022. The outcomes will be made available to UNODA, including recommendations on how to address identified challenges.

In conclusion, existing laboratory exercise schemes will advance further and new ones will start soon. Moreover, a number of practical activities of relevance for designated laboratories are on-going or are about to start. This is excellent news, especially when considering the difficulties and challenges posed by the on-going pandemic situation.

In more general terms, this sixth UNSGM Designated Laboratories Workshop was another significant step by this dedicated community to engage and redouble efforts to move towards an operational and fit-for-purpose network of trusted laboratories for the UNSGM. Within the concert of all the efforts to strengthen the operational capacity and capability of the UNSGM, the support, coordination and outreach of UNODA will be central to sustain interest and attract funding.

Finally, the need for a UNSGM designated laboratories network is apparent. There is increasing clarity about the specific parameters that need to be fulfilled and work is to continue now on the in-depth details of technical procedures, tools and criteria. The Swiss workshop series will continue to serve as a platform for feedback and cross-talk between different projects, to ensure that all these activities move towards a compatible system and common approach, whilst maintaining the right balance between standardisation and flexibility. To that end, the seventh UNSGM Designated Laboratories Workshop will take place from 14 – 16 September 2022.

1. Introduction

This report presents the outcomes of the sixth Swiss UNSGM Designated Laboratories Workshop organised by Spiez Laboratory on a network of trusted laboratories designated under the United Nations Secretary-General's Mechanism (UNSGM) to investigate allegations of the use of chemical, biological and toxin weapons. It took place from 16 to 17 September 2021 under conditions imposed by the on-going COVID-19 pandemic. Whilst a few session chairs, presenters and support staff travelled to Spiez to conduct the proceedings, most presenters and participants joined the workshop remotely. Given these constraints, the agenda was more condensed than at previous workshops. At the same time, this format allowed for a broader participation with 75 participants from 18 Member States as well as the UN Office for Disarmament Affairs (UNODA), the Organisation for the Prohibition of Chemical Weapons (OPCW), the World Health Organization (WHO), the World Organisation for Animal Health (OIE) and the International Criminal Police Organization (INTERPOL) joining the discussions.

This workshop series is part of a wider effort to strengthen the operational capacity and capability of the UNSGM. The Mechanism depends heavily on what Member States invest into its key components, such as training of qualified experts to conduct investigations, expert consultants to advise the Secretary-General on key issues, and laboratories nominated by Member States to conduct analyses of samples and perform other tasks.

The UNSGM can rely on the capabilities of the OPCW with its Designated Laboratories to investigate alleged chemical weapons uses. The situation is different in the biological field: although Member States have nominated 83 laboratories to the UNSGM laboratory roster,[2] efforts to ensure the validity and accuracy of their analytical methods - through participation in inter-laboratory calibration studies, such as external quality assurance exercises (EQAE) - have only begun in recent years. These activities are essential for the credibility of the UNSGM. Whilst many high-quality bioanalytical laboratories exist worldwide that can analyse human, animal and plant pathogens as well as toxins, UNSGM designated laboratories should meet additional requirements:

Scientific competence and technical skills to identify and characterise the target agents of a particular investigation, which may go beyond the capabilities of laboratories in the public health domain, since certain agents of relevance to UNSGM investigations are of little interest to public health;

Ability to meet forensic and procedural standards, including the implementation of an unbroken chain of custody;

Reporting skills and tools fitting the requirements of a UNSGM investigation, since these differ from and exceed those required for other laboratory investigations;

Furthermore, it would be desirable that UNSGM designated laboratories would have the widest possible geographical distribution.

Setting up a network of such laboratories is a step-by-step process of engaging with laboratories nominated by Member States as well as other relevant laboratories, and of clarifying the requirements that designated laboratories should meet to be fit for purpose.

[2] https://www.un.org/disarmament/wmd/secretary-general-mechanism

These discussions began in 2015,[3] and Spiez Laboratory offered its workshops as a platform for consultation and planning. Since 2017, several Member States[4] have organised exercises to gain practical experience and further develop the concept of the network. In accordance with the UNSGM Guidelines and Procedures, these activities support the work of UNODA, which includes outreach to the laboratories nominated to the UNSGM roster, increasing the geographical breadth of the roster, and facilitating training and exercises.

These discussions have clarified the various stages of a forensic investigation from identification to characterisation and attribution, and have highlighted the key requirements for a UNSGM designated laboratories network:

- Ability to unambiguously identify the causative agent of an alleged incident involving a biological or toxin weapon, including:
    - A well-documented, unbroken chain of custody,
    - The use of multiple, orthogonal analytical techniques,
    - Accreditation of methods to internationally accepted standards,
    - Agreed acceptance criteria for the different methods employed,
    - Adherence to the highest standard of biological safety,
    - The ability to differentiate between natural events and manmade outbreaks;
- Attribution usually requires additional types of analysis to link a causative agent to a source or particular actor;
- Access to curated reference databases;
- Use of open-source software;
- Methods validation and, as necessary, standardisation, including recommended operating procedures or, perhaps, standard operating procedures.

Previous discussions have also identified challenges with regard to sample collection and transfer, and the interaction between the field investigation teams and the laboratories selected to perform sample analysis. These included:

- The development of technical guidelines for sample collection in an investigation, and for sample transfer from the site of collection to the designated laboratories;
- Concepts for the interaction of the investigation team in the field and the laboratories selected for authentic sample analysis;
- The need to embed laboratory competence in investigation teams;
- Depending on the Mission scenario, the need for a designated laboratory operating as a secure work area for sample processing as well as the provision of assistance / consulting services, and in this context the possible role of mobile labs.

There are virtually countless biological and toxin agents, thus prioritisation is indispensa-

[3] Previous workshops that discussed the idea of a UNSGM designated laboratories network were held in Stockholm (June 2015), Umeå (October 2016), Geneva (April 2016) and Spiez (November 2015, June 2016, June 2017, September 2018 and September 2019). Complementing these discussions were a workshop on toxin analysis (Berlin 2020), and toxin analysis exercises organised by the OPCW (2016-2020). Most recently (2021), the OPCW Scientific Advisory Board has established a Temporary Working Group on biotoxins analysis.

[4] In 2017, Germany started its RefBio project which involves EQAE and workshops in the areas of bacteriology, virology and toxinology. Denmark and Sweden, with financial support from the United States, organised a dry lab genomics analysis exercise in 2018.

ble. Developing a UNSGM designated laboratories network requires decisions about a starting point and an initial breadth of scope to aim for. A number of criteria have been suggested, including ease of production of the target agent, past history of weaponisation or evaluation in biological weapons programmes, pathogenicity / toxicity / activity, and properties such as stability, detectability, and availability of effective countermeasures. In addition, there is the question of balance between present-day DNA sequencing techniques and methods to characterise the microorganism, and the differing analysis demands of small molecules versus high molecular weight toxins. Furthermore, EQAE should at some point include live agents, since the gold standard of identification consists of isolation, cultivation and characterisation, while bearing in mind that isolation of a cultivable agent after a biological weapons incident may not be possible.

Another challenge identified in previous discussions was the reporting of analytical results. Whilst scientific and public health laboratories routinely report their findings, reporting in the context of a UNSGM investigation poses additional requirements: it must be sufficiently robust to withstand technical scrutiny in a wider political and legal context. The report must demonstrate the scientific competence of the laboratory, provide evidence of an unbroken chain of custody, and show that stringent quality assurance has been applied. It is important for the report to describe the findings as specific as the deployed capability allows, as well as stating the limitations of methods and acceptance criteria applied.

Whilst experience of the OPCW can be helpful in this respect, the reporting system of the OPCW cannot be transferred one-to-one and used by the UNSGM for reporting in biological investigations. Instead, previous discussions concluded that it would be desirable to develop a harmonised UNSGM designated laboratories reporting template.

As the efforts of creating the UNSGM designated laboratories network have moved from conceptualisation to practical steps, work has focused on training, EQAE, methods validation, and the development of proposals for recommended operating procedures, guidelines and templates. These practical steps have highlighted the need to further clarify terminology for the tasking of laboratories as well as reporting: how to substantiate laboratory findings, express levels of confidence, and present laboratory findings without prejudging the conclusions of an investigation? Particular care needs to be taken to interpret results indicative of a deliberate agent release, and for attribution purposes. At the same time, these practical exercises and discussions also provide a better picture of how designated laboratories may be selected for a particular investigation, and what administrative issues, such as technical agreements, still need to be developed to this end.

Finally, it is important to increase the geographical spread of laboratories participating in these activities and to secure sustainable funding. The benefits of participating in the development of the network are becoming ever more apparent. Not only does it enhance the operational capacity and capability of the UNSGM, it also creates opportunities for improvement, self-assessment and benchmarking. Laboratories gain confidence, and collaborations between them facilitate access to critical assets, such as databases, reference materials, analytical methods and expertise.

The sixth UNSGM Designated Laboratories Workshop in Spiez was a further milestone on this road towards a trusted UNSGM designated laboratories network. The following chapters of the report summarise the discussions, its main findings and recommendations.

2. Laboratory exercises

The workshop received an update on past activities and plans under Germany's RefBio project. Subsequently, workshop participants were informed about an international laboratory exercise planned by the State Key Laboratory of Infectious Disease Prevention and Control of China CDC, as well as a dry lab exercise on viral genomics planned by Denmark, Germany and Sweden.

Germany's RefBio Project

The RefBio project – 'Germany's contribution to strengthening the Reference Laboratories capacity of the UNSGM' – was initially approved from 2017 to 2020, with a one year extension due to the pandemic situation. It is funded by the German Federal Foreign Office and implemented by the Robert Koch-Institute (RKI) in Berlin. It aims at furthering laboratory capabilities for the UNSGM on a broad geographical level and covers the fields of virology, bacteriology and toxins. RefBio has recently been extended for another three years – from 2022 to 2024.

The project helps participating laboratories evaluate their capabilities based on their performance in EQAE. Laboratories can identify areas of improvement and assess how chain of custody requirements are being met. The project facilitates trusted exchange of results and best practice between participants. In the longer run, it will also help in exercising and improving recommended procedures, for example for sample transfer, chain of custody, or analytical results reporting.

An important aspect of the project is to develop recommendations for minimal and optimal requirements of designated laboratories – a tool that Member States may then use when nominating laboratories to the UNSGM roster. The project outcomes also increase the knowledge about the capabilities and specialisations of UNSGM bioanalytical laboratories, which can assist the Secretary-General and facilitate decisions in selecting laboratories for an investigation.

Since its start, project RefBio has so far conducted ten EQAE:

- Four EQAE on bacteria (2017, 2018, 2019, 2021) - Targets: *F. tularensis, Y. pestis, B. anthracis;*
- Three EQAE on viruses (2018, 2019, 2021) - Targets: Orthopoxviruses;
- Two EQAE on toxins (2019, 2021) - Targets: Ricin (*R. communis)*, Botulinum neurotoxins (*C. botulinum*);
- One EQAE on SARS-CoV-2 (2020).

Annual workshops were conducted to share experiences and best practices, and undertake planning and evaluation of these laboratory exercises. The activities were closely coordinated with other measures to strengthen the operational capacity of the UNSGM. Topics under discussion included:

- Results of conducted EQAE;
- Upcoming EQAE;
- Roles of designated laboratories in the UNSGM;
- Minimal and optimal requirements of UNSGM designated laboratories, nomination guidance for Member States;
- Chain of custody in UNSGM designated laboratories;
- Results that might be expected from UNSGM designated laboratories (depth of analysis);
- Reporting of results by UNSGM designated laboratories (reporting templates);
- Needs of laboratories to exchange best practices and methods;
- Training needs of designated laboratories with limited capabilities;
- Interaction of laboratories with the on-site investigation team;

- And with a long term view: Development of an algorithm for assessing laboratory capabilities and to extract recommendations to UNODA.

Interest in the project and participation of laboratories from different Member States and regions has steadily increased since its inception, although South America, Africa, the Middle East and parts of Asia are yet to engage more significantly in the project.

During 2020, in response to the COVID-19 pandemic, an EQAE on SARS-CoV-2 and other coronaviruses was conducted. 32 laboratories from 20 Member States, amongst them 17 UNSGM roster laboratories and 15 laboratories nominated by four Member States on an *ad hoc* basis, tested their capabilities to identify and characterise SARS-CoV-2 and other human coronaviruses in non-infectious 'clinical' swab and plasma samples. The participating laboratories were requested to identify swab samples that tested positive or negative for SARS-CoV-2 using PCR or another method of their choice, to differentiate SARS-CoV-2 from other coronaviruses, and to analyse the genomes of SARS-CoV-2 with SNP comparison (whole genome sequencing). The viral targets included SARS-CoV-2, SARS-CoV, and NL63.

SARS-CoV-2 was identified correctly by all participating laboratories. NL63 was identified correctly by 20 of the 30 participating laboratories,[5] and SARS-CoV by 22 of 29 participating laboratories. Most laboratories used PCR and next generation sequencing for identification. 17 participating laboratories performed DNA sequencing for characterisation, whereas eight of them were able to identify all SNPs correctly.

With regard to the plasma samples, laboratories were requested to identify samples with SARS-CoV-2 specific antibodies using serological methods of their choice, to identify samples with neutralising activity for SARS-CoV-2 using functional methods of their choice, and to sort the samples according to reactivity or neutralising activity.

While not all assays correctly identified the targets, all laboratories were still able to identify the samples with specific antibodies correctly. Relative reactivity differed regarding the target antigen. For assessment of neutralising activity, most participating laboratories applied cell-based SARS-CoV-2 neutralisation assays. Almost all participating laboratories identified the SARS-CoV-2 neutralising samples correctly.

The participating laboratories rated the exercise as successful and of high interest to them. The overall level of difficulty was considered medium, with identification of SARS-CoV-2 in the swab samples being the easiest, and characterisation of the swab samples the most difficult task.

For 2021, the RKI plans three more EQAE: a bacterial (*Brucella* species, including live agents), a viral (unknown haemorrhagic fever virus), and a toxin (botulinum neurotoxin) exercise.

The bacterial EQAE will use a fictitious scenario involving clinical, environmental and food samples, including one live sample. The tasks for the participating laboratories will include, in order of increasing difficulty, identification of the *Brucella* positive samples, identification of the *Brucella* species, identification of the bacterial strain, and finally, further molecular characterisation.

The viral EQAE will involve four sets of lyophilised non-infectious clinical samples. Laboratories will be tasked to detect an unknown virus, prepare a case report and characterise the virus with next generation sequencing. Possible targets for identification include Chikungunya virus, Dengue virus, Ebola virus, Hantavirus, Crimean Congo-Haemorrhagic fever virus, Lassa virus, Rift Valley fever virus, West Nile virus, Yellow fever virus and Monkeypox virus.

The toxin EQAE will involve six sets of samples containing active clostridial neurotoxins

[5] Not all 32 laboratories participated in all parts of the exercise.

(clinical, environmental, food). With increasing levels of difficulty, participants are to identify botulinum neurotoxin positive samples, identify the sero-/subtypes, and assess the activity.

The starting dates were communicated as 5 October (toxin EQAE) and 18 October 2021 (bacterial and viral EQAE). Three to four weeks have been allocated for analysis and reporting. The reports and certificates will be provided in February / March 2022, and meetings with all EQAE participants will be held in March / April (toxin EQAE) and May 2022 (bacterial, viral EQAE). 30 laboratories have registered for the bacterial EQAE, 25 for the viral EQAE, and 17 for the toxins EQAE.

A major development brought to the attention of the workshop participants was the decision to extend the RefBio project for another three years, from 2022 to 2024. The project team remains essentially the same. Annual workshops of participating laboratories to share experiences and best practices, and to conduct planning and evaluation will continue. So will the annual EQAE in all three disciplines, and the provision of training to laboratories nominated to the UNSGM roster.

A new element of the project will be the setup of a curated reference genome database for use in forensic profiling of bacteria. This will include:

- Defining reference strains and sequencing strategies;
- Integration of sequences from public databases such as GenBank (criteria to be developed);
- Setup of a secure IT-infrastructure for hosting the database, and bioinformatic pipelines for analyses.

This initiative reflects findings from previous discussions about the potential of next generation sequencing as a tool for UNSGM investigations, and the need for curated reference databases.

The RefBio project will also establish an advisory group, and develop a laboratory reporting sheet tailored to the specific aspects of UNSGM investigations.

Planned laboratory exercise organised by the State Key Laboratory of Infectious Disease Prevention and Control of China CDC

A new initiative presented at the workshop was a sand-table laboratory exercise planned for 2022 by the State Key Laboratory of Infectious Disease Prevention and Control (SKLID) of the China Centre for Disease Control (China CDC): Identification of a currently unknown pathogen, which has not been described previously and is presumed to be the causative agent of a potential international epidemic (Disease X), and investigation of its animal origin.

Established in 2005 after the SARS outbreak, SKLID is well suited to run such an exercise, as it aims at first class disease prevention and control based on excellence in research. Its areas of activity include molecular typing and phylogenetic analysis, mechanisms of emerging infectious diseases, discovery of new bacteria and viruses, surveillance, diagnostics and vaccine development. SKLID combines responsibilities in field investigations of infectious disease outbreaks in China with applied scientific research. Its laboratory capacity includes systems and platforms for multimodal *in vivo* imaging, mass spectrometry, electron microscopy, flow cytometry, and high content imaging and analysis. SKLID operates seven BSL-3 laboratories working with *Y. pestis*, *B. anthracis*, *F. tularensis*, *M. tuberculosis*, *Brucella*, *Rickettsia*, *Anaplasma*, SARS CoV, SARS-CoV-2, *Bunyavirus*, HIV, and newly isolated viruses. Between 2012 and 2021, it has named or discovered more than 60 new bacterial species and sequenced more than 1,000 viruses. Furthermore, scientists from SKLID participated in the dry lab exercises organised by Denmark and Sweden, as well as the EQAE organised under Germany's RefBio project.

The exercise scenario includes an outbreak of a disease of unknown aetiology in a large city in Eurasia, involving fever, headache and cough. Over a seven-month period, some 50 patients aged between 1 and 80 years were admitted to hospitals, some with a history of animal contact. Laboratory tests showed normal leukocyte levels, low neutrophil levels,

and normal C-reactive protein. Examination of cerebrospinal fluid showed low leukocytes and increased total protein. All patients tested negative for a broad spectrum of pathogens. A potential new viral pathogen causing respiratory disease or meningoencephalitis was highly suspected as the causative agent. The circumstances suggest a pathogen of animal origin.

The exercise will include two tasks: identification of the potentially new pathogen, and investigation of its animal origin. For identification purposes, three sets of samples will be provided, including samples positive or negative for inactivated target virus and one negative control sample. These will be clinical samples from diseased patients and healthy individuals, and include extracts of nasopharyngeal swabs, faecal swabs and blood. Participating laboratories are asked to obtain the complete genome sequence of the new virus and to present phylogenetic analysis results based on the genome.

To investigate the animal origin of the new pathogen, four sets of samples will be prepared to include liquid extracts of intestinal contents, blood, and organ samples from three wild animal species and one vector, as well as one negative control. Participants are tasked to provide the complete genome sequence of the new virus in those animal and vector samples, as well as the phylogenetic analysis results based on the genome and nomenclature conclusion. Participating laboratories are free to choose the analytical methods, based on their capabilities and capacities, and an appropriate workflow.

Participation in the exercise is coordinated by UNODA; the exercise is planned to commence in March 2022.

Planned dry laboratory exercise on genomic sequence data from viruses

Earlier dry lab exercises conducted in a project by the Technical University of Denmark (DTU) and the Swedish Defence Research Agency (FOI), with financial support from the US Department of State had identified a number of challenges:

- The availability of bioinformatic pipelines and tools as well as curated databases;
- Expertise in clinical and virological issues, adequate sensitivity and specificity of methods, and contamination management;
- Technical competence in forensics, including the characterisation of an identified agent as “novel / emerging / natural”, the detection of signs of genetic engineering or synthesis, as well as experience in genetic attribution.

Building on these past activities, RKI, DTU and FOI are now preparing a two-year project of dry lab EQAE with focus on the detection and characterisation of viral pathogens as biological weapons using DNA sequencing. Funding is provided by the US Department of State.

Two exercises are planned, both simulating a UNSGM investigation of a biological weapons use allegation in a long-term conflict scenario. The first exercise will use a fictitious outbreak of a virus among humans and in wildlife. Both tests will involve five datasets, allow six weeks for analysis, and the sequencing techniques will include Illumina and Nanopore technology. The first EQAE commenced on 20 September 2021.

Participants of the first EQAE will be tasked to identify the virus reads from the samples, to reconstruct partial or full genomes of the viruses for characterisation, and to investigate any peculiarities in the virus genomes that may point towards a biological weapons use. The set will include samples taken from the outbreak site, a sample related to a previous outbreak and animal as well as cell culture samples taken at a suspected laboratory.

Invitations to this first EQAE were publicised in the UNSGM newsletter and via various networks. The download link was sent out on 20 September and results are expected by 1 November 2021. A report on the exercise is

planned for March 2022, in time for the second EQAE, which will commence in May 2022.

The level of participation (94 laboratories have signed up, including 17 UNSGM roster laboratories) is testimony to the growing strength and breadth of the next generation sequencing capacity available to the UNSGM.

3. Interfaces of laboratories

Under the theme of laboratory interfaces, the workshop addressed how UNSGM designated laboratories can be involved in the upcoming capstone exercise, and received a briefing on the Temporary Working Group of the OPCW SAB on biotoxins analysis.

Involving UNSGM roster laboratories in the capstone field exercise and lessons from the pre-deployment table-top exercise

The capstone exercise is part of a further project implemented by the RKI to strengthen the UNSGM and complements other activities, including basic and refresher trainings, e-learning, and table-top mission planning exercises. It runs from 2019 to 2023 and focuses on qualified experts nominated to the UNSGM roster. The capstone exercise is being implemented in cooperation with UNODA and is funded by the German Federal Foreign Office.

A first activity was a five-day virtual table-top exercise of the pre-deployment activities of a simulated UNSGM investigation. More than 50 participants, including observers, interacted across several time zones via an online conferencing platform using a remote exercise management system. The table-top exercise covered the mission planning phase in accordance with the UNSGM Guidelines and Procedures, including the development of a command-and-control plan, an interview plan, a sample collection plan, and a requirements and logistics plan.

In the context of developing the sample collection plan, the team of qualified experts consulted with the participating designated laboratories:

- What is the best choice of a secure work area for aliquoting and preparing samples to be sent to designated laboratories?
- Are import permissions for samples required?
- Can the chain of custody be maintained in the secure work area?
- Which procedures should be used to transfer samples to the designated laboratories?
- Which capabilities do the designated laboratories have to confirm and characterise *Y. pestis?*
- What is their status regarding accreditation under ISO 9001 and 17025?
- Can the designated laboratories maintain the chain of custody?
- What sampling guidance is routinely provided for samples collected to confirm *Y. pestis* (preferred sample types, volumes, media, storage)?
- Do the designated laboratories have any experiences with specific in-field testing devices for *Y. pestis*?

The sampling strategy developed includes the collection of a minimum of three samples (preferably four), with three types of samples: environmental, biomedical, and veterinary. Blank and control samples, too, will be required. Samples will be labelled with unique barcodes. Aliquoting should preferably be done in a secure work area, and packaging should use IATA packaging and meet the criteria for Category A samples. Two UNSGM team members should accompany the sample during transport to ensure chain of custody. Field analysis was considered useful only for health and safety reasons and for informed sample collection, but not as a means of evidence collection. The methods for laboratory analysis would be consulted with the designated laboratories. The sample collection plan would be reviewed and revised as necessary, based on additional information received during the pre-mission phase and on site.

A number of lessons have been learned in the table-top exercise that will inform future exercises and particularly the preparation of the full-scale exercise:

- Importance of a close cooperation between all involved stakeholders;

- Significance of established trust in the mission team based on previous training experience;
- Need for flexible planning;
- The virtual format provided a new way of training, but has also disadvantages (e.g. reduced personal interaction).

The final step will be the conduct of a full-scale field exercise of a UNSGM investigation, which, due to the pandemic, had to be postponed to spring of 2022. This exercise will use the revised plans that were developed during the table-top exercise, and identify gaps that need to be addressed in the future. It aims to involve all relevant stakeholders to simulate the complexity of a UNSGM mission.

Issues that may require further attention are a discussion on which analysis methods should be covered by the scope of accreditation of a designated laboratory and to what extent chain of custody procedures at designated laboratories can be guided / standardised.

The OPCW SAB Temporary Working Group on the analysis of biotoxins

In an effort to further align the work in support of the UNSGM with the efforts of the OPCW to develop its capacity in toxin analysis, the workshop received a background briefing on the newly formed Temporary Working Group (TWG) of the OPCW Scientific Advisory Board (SAB) on the analysis of biotoxins.

The SAB is an independent advisory body for the OPCW Director-General and through him the OPCW policy making organs and Member States. A TWG is established by the Director-General to address specific issues within specific timeframes. Any TWG includes SAB members as well as external experts with specific expertise in the area under discussion. A TWG can call upon guest speakers to educate it on particular technologies, research directions and approaches. It can also engage and interact with the Technical Secretariat, including the OPCW laboratory.

The TWG on biotoxins analysis has been set up with funding from the European Union. Its work started in January 2021 and will continue for a minimum of two years. It is tasked to:

- Review the science and technology relevant to the analysis of biotoxins and to consider what needs to be taken into account in investigations of their alleged use;
- Identify capabilities, skill sets, and equipment that would augment and strengthen the Technical Secretariat's capabilities in this respect.

Nine Members of the SAB participate in this TWG, with Daan Noort from the Netherlands acting as chair and Christophe Curty from Switzerland (SAB chair) as well as Andrea Leisewitz from Chile as vice chairs. Six external experts from Canada, Germany, the Russian Federation, Sweden, the United Kingdom and the United States have also been appointed.

The TWG bases its work on the understanding that biotoxins are "substances produced from biological sources (e.g. animal, plants, microorganisms) that have deleterious effects on a living organism" (Clark et al. 2019). Biotoxins fall within the scope of prohibitions of both the Chemical Weapons Convention and the Biological and Toxin Weapons Convention. Some toxins have been weaponised in the past (ricin and botulinum toxin are examples), some have attracted the attention of terrorists (exemplified by the ricin case in Cologne, Germany, in 2018). At the same time, several toxins are of great commercial and/or scientific interest, examples being the use of botulinum toxin in clinical and cosmetic applications and the use of toxins in fundamental research as well as medicine.

The TWG has formed five sub-groups to study the following questions:

Subgroup 1: What are the underlying requirements for the analysis of biological toxins in order to investigate alleged use of toxic chemicals as weapons?

Subgroup 2: What classes of biological toxins are most likely to be relevant in investigations of alleged use? Are there other relevant compounds of biological origin that should also be considered based on their potential for misuse or technological change associated with them?

Subgroup 3: What are the technical requirements for analysis of the most relevant types of biological toxins? This may include: analytical approaches needed for unambiguous identification; instrumentation and/or procedures that should be standardised across labs; analytical criteria to match forensic requirements; the role and utility of degradation products and other markers; the role of biomarkers and biomedical samples.

Subgroup 4: What are the analytical standards and requirements of other international and national investigative authorities and how do these compare? How can programs of analytical exercises conducted by different networks of laboratories be coordinated or harmonised (e.g. with regard to quality system requirements)?

Subgroup 5: What institutional or legal measures need to be established to facilitate cooperation between the OPCW and other organisations working on the development of capabilities for analysis of biological toxins?

Based on the outcomes from the five subgroups, the TWG will prepare a report on its findings and recommendations for the SAB. On approving the report, the SAB will prepare its own assessment of the matter and submit the report to the OPCW Director-General. It may also, if the Director-General so requests, prepare advice for the Technical Secretariat on methodologies, procedures, technologies and equipment for the analysis of biotoxins. In addition, the Director-General might pose additional questions to the TWG.

So far, two half-day virtual TWG meetings have been conducted. The reports are available on the OPCW website.[6] A further meeting was announced for November 2021.

This briefing was a welcome contribution to share information about on-going activities that complement the work towards a UNSGM designated laboratories network.

[6] https://www.opcw.org/resources/documents/subsidiary-bodies/scientific-advisory-board

4. Laboratory reporting

The importance of developing guidance and templates for the laboratory reporting of results to a UNSGM mission has been highlighted at several previous occasions. The sixth UNSGM Designated Laboratories Workshop received a briefing on experiences from bio-forensic casework, and on a proposed reporting template developed under the RefBio project.

Reporting practices of forensic laboratories are well established and could guide the development of UNSGM forensic reporting. Such reporting is discipline-specific and strictly oriented on the questions posed by the investigation team. An investigation may require different types of analyses from different laboratories, resulting in several different laboratory reports each addressing distinct questions. The items to be tested by the laboratories must be well defined and reports must address the specific questions posed to them. Any analytical work carried out under accredited conditions should be clearly stated as such by the laboratories.

A forensic report is a summary of what was done by the laboratory, with what and how, and what were the results of the tests conducted. It should state:

- what was received;
- what was analysed;
- what analysis was performed;
- the result for each analysis conducted; and
- provide a summary of the results.

The laboratory retains all information that was needed to support the conclusion of the report. Instrument data and supporting information are not part of the laboratory report. However, the laboratory should be able to provide supporting information, if so requested by the investigation team. Supporting information likely includes:

- A copy of the laboratory's accreditation certificate;
- Copies of all standard operation procedures used to perform the analysis;
- Copies of training documentation for staff performing the analysis;
- Copies of results from quality assurance exercises;
- Copies of assay validation reports and data for the assays that were performed as part of the analysis;
- Copies of raw data used to support the conclusions in the report;
- Identification of the database that was used to support the conclusions in the report;
- A description of the software tools used to support the analysis (including the sources for commercial tools, and product specifications for custom tools).

In summary, a forensic laboratory report is a statement of facts by the laboratory, based on the analysis it performed on the evidence it received. It needs to contain all the information that is required to support the analysis that has been requested by the investigation team. It is therefore important to clarify between the investigation team and the laboratory precisely what the investigators are seeking. Any supportive information may be submitted, if so requested by the investigation team. Each analysis conducted by the laboratory must have a report of the findings, all analyses to be conducted should be agreed to in advance with the investigation team, since some analyses will destroy or consume the sample, which may limit further investigation options.

Based on these principles, and on experience from previous EQAE, efforts have been made under the RefBio project to develop templates for laboratory reporting. Experiences of the OPCW have also been taken into account, whilst recognising the differences between chemical and biological investigations.

A first consideration was on the elements that have to be included in a laboratory report to an investigation team, and which supportive information could be provided separately as attachments or upon request.

Second, an iterative refinement of laboratory report templates should take place based on feedback from participants in EQAE. Ultimately, a template containing all options to address investigations involving bacteria, viruses and toxins should be developed.

Third, the development of such a template could incorporate elements from law enforcement reports, Appendix C of the UNSGM Guidelines and Procedures, feedback from laboratories participating in RefBio EQAE as well as input from the newly established RefBio advisory group.

A draft table of content and related data tables of the draft laboratory report template were presented at the workshop. These included:

- Identification of the commissioned analytical institution and further detail regarding the institutional entities involved in the sample analysis;
- Results of agent identification and characterisation, including:
    - Summary data on sample identification, identification of any subsamples, methods used, agents identified and estimated concentrations as well as contamination levels,
    - Data on agent isolation (for bacteria and virus analyses);
- Results of agent characterisation, broken down by typing methods, identification of virulence genes / epitopes, functional activity (infectivity, toxicity), and identification of other relevant peculiarities;
- Responses to specific questions raised by the investigation team;
- Details of the methods applied, grouped into isolation / purification methods, amplification-based assays, next generation sequencing and data analysis, immunological assays, mass spectrometry (non-functional), functional assays, and other methods;
- Information on the chain of custody.

Additional details and technical data would be made available upon request by the designated laboratory. All original analytical data would be securely stored in a protected area.

Using the draft template in the latest EQAE has already generated valuable feedback from participants and has highlighted a number of questions:

- Is it possible to collect all samples (including unknowns, negative controls, known negatives) in the field? This is scenario dependent and may not be possible in all cases, e.g. if the disease is endemic at the location under investigation;
- Are all sections of the laboratory report template relevant for the conduct of EQAE? Some sections may only be relevant in an actual investigation, but in order to raise awareness and for practice purposes, all sections are nonetheless included;
- Can the summary table on sample reception and sample workflow be improved?
- Methods accreditation is important, but at the moment methods are often not accredited;
- Next generation sequencing should be included in the tool kit;
- Management and access to data is often not secure at this stage;
- Curated databases for reference data are not yet available;
- Is it advisable to use open-source software?
- Should laboratories state their level of confidence in the results reported?

The development of the template will be pursued further in 2022, supported by the

RefBio advisory group that would bring together interested participants in the project, certain external experts, and UNODA. Its utilisation in the planned “Disease X” exercise organised by SKLID is under discussion.

5. Sampling guidance

Participants of the 2018 UNSGM Designated Laboratories Workshop recognised the necessity to address the interaction of investigation field teams and designated laboratories, especially concerning appropriate sampling tools, sample types, and sample transfer. Subsequently, certain tools for sample collection were reviewed. Since then, a small working group has been formed, needs have been outlined, and existing protocols have been reviewed and amalgamated into draft recommended operating procedures and associated guidance documents.

At this stage, recommended operating procedures with associated aide memoires and field guides have been prepared for environmental biological sampling as well as for the preparation of biological samples for international shipment. Both documents have the form of guidance documents for the Head of Mission of a UNSGM investigation. Biomedical sampling has been earmarked as a next target for a draft recommended operating procedure.

With regard to sample collection, a number of issues, some already identified at previous workshops, were highlighted:

- All samples must be collected using appropriate biosafety measures;
- Consideration must be given to identifying the best samples for assessment of the alleged threat;
- Known gold standards, in-field testing, reliance on laboratory expertise, and local epidemiology are important considerations;
- It is important to discuss the sample collection strategy with the laboratories selected for analysis.

The draft recommended operating procedure outlines a proposed composition of an environmental sampling team, including roles and duties. More than one role may be assumed by one individual, with the evidence collector and assistant being the two core roles. Depending on the context, the team may also require expertise in handling and disarming explosive devices and substances.

The draft recommended operating procedure contains guidance on sample splitting or the collection of replicate samples, on the numbers of sample splits / replicates needed, and on risk assessment, including Explosive Ordinance Disposal and mixed threats.

The sample collection process is broken down into nine steps:

1. Taking a photograph of the exhibit / sample area;
2. Completion of the sample data sheet to include lot numbers of any solutions utilised;
3. Collection of the sample in an appropriate manner using a sterile single-use tool;
4. Placement and sealing of sample / exhibit within a primary container;
5. Placement and sealing of primary container into secondary container;
6. Decontamination of secondary container by wiping or dipping into an appropriate decontaminant;
7. Change of gloves as well as sample collection tools (single use) between each sample collected;
8. Transfer of all samples from the scene in decontamination bucket to the clean / dirty line where the samples are removed and sealed into clean evidence bags;
9. Bagging of the sample data sheets (if paper) in single flat bags readable from both sides, followed by decontamination. Electronic data sheets or digital photographs of paper data sheet can be recorded alongside taking photographs of the exhibit / sample area.

Types of environmental samples of potential interest to a UNSGM investigation were identified. They include powders, water / liquids,

microbiological culture media, stains (microscopic slides), swabs from clothing, carpets, paper, walls and wallpaper, aerosol samples, dead animals, ticks and other arthropod vectors, air purification cartridges and HEPA filtration units, food, soil, water / snow, vegetation, munitions, and clothing.

The draft recommended operating procedure is a technical guide for how to plan, manage and conduct the collection of environmental samples related to a biological incident. The guide is not a recommended operating procedure in the strict sense of the word, but it provides options for sample collection for various materials of potential interest for an investigation. It is also not a comprehensive evidence management plan or sampling strategy. Such a document that accounts for the complexity of a mission and its unique circumstances would need to be developed by the investigating team.

The development of this draft recommended operating procedure creates additional training possibilities for personal protective equipment, safety as well as sample collection, and for updating the equipment list. It also confirms the need for additional guidance and complex decision-making tools.

With regard to the preparation of biological samples for international shipment, the workshop participants were briefed on the packaging and labelling requirements for infectious samples affecting humans (UN 2814), including a UN-type packaging box and the related shipper's declaration.

Issues that need further attention include the collection of different kinds of samples (including unknowns, negative controls, known negatives). It was questioned whether the collection of environmental blanks was actually necessary, and it was felt more important to ensure that the right sample was collected and that the sampling material was demonstrably clean. It is equally important to ensure that digital photos record a full set of metadata with camera details, location and time of capture, and image data in RAW image format to substantiate the authenticity of the images taken.

6. Sample transfer

A final theme was the transfer of samples, since Member States are committed to run scenario-based table-top exercises on the international transfer of samples for analysis based on different realistic scenarios. This recognises difficulties encountered in recent years with regard to sample transfers during public health emergencies.

Coordinated by the US Department of State, a virtual table-top exercise is being prepared. The exercise will explore political, legal, regulatory, and technical challenges that could be encountered when moving a biological sample across international borders, and discuss potential solutions. It applies a multi-step scenario to examine as many aspects of the transfer process as possible.

The legal and regulatory challenges include the Nagoya Protocol, ownership rights, access and benefit sharing laws, authorised uses of sample material, coordination with government officials for approval of transport, export / import controls, overflight restrictions, and other national regulations.

Technical challenges to be assessed include proper packaging, labelling, documenting, handling, chain of custody, and availability of transport. Issues related to sample collection, temperature control, sample storage and investigation procedures, will not be addressed in this exercise, although they may affect sample transportation processes.

The different steps to be exercised include transport of the sample from a local storage site to an airfield for export, physical transport to another country, import, transfer from the airfield to the designated laboratory, and possible shipment to yet another designated laboratory for analysis. Multiple countries are included in the scenario, and various types of samples are being considered (biomedical human and animal samples, dissemination device, protective equipment, food / water, crops / vegetation).

Participants with the following backgrounds will be invited:

UN staff and experts involved in strengthening the operational capability of the UNSGM;

Transportation / logistics experts with competence in international transportation of infectious materials, import / export controls, and shipment / handling of dangerous goods;

Laboratory officials knowledgeable in standard operating procedures, administrative protocols, as well as equipment and specimen management;

Public health officials and scientists;

Legal experts with expertise in the international transfer of biological materials;

Law enforcement officials.

The table-top exercise is planned for the end of 2021 or early 2022. A report will be issued and made available to UNODA, outlining the exercise and its objectives, describing potential pitfalls in the transfer process at various stages, and recommendations on how to address these challenges as well as outline possible mitigation strategies.

7. Conclusions and next steps

This sixth UNSGM Designated Laboratories Workshop was another step towards an operational and fit-for-purpose network of trusted laboratories for the UNSGM. The need for such a network is no longer in question, the parameters for what a fit-for-purpose UNSGM designated laboratories network should look like are becoming clearer, and work is increasingly getting into the in-depth details of technical procedures, tools and criteria.

It has become apparent that the range of capabilities required for biological / toxin investigations under the UNSGM must be wide-ranging. This on-going series of workshops has focused on bioanalytical laboratories. These are of central importance, but they are not the only laboratory capability a UNSGM investigation may need. Classical forensics or weapons characterisation are other examples for the kind of support a UNSGM mission may need.

Even in the context of bioanalytical laboratories, the range of methods required is very wide, ranging from bioinformatics and next generation sequencing to methods from toxinology, serology, microscopy and other disciplines. Exercises to develop criteria and parameters for these types of laboratory analyses are underway, and so are efforts to develop the necessary procedures, guidelines and templates. It will thus be important to ensure that all these activities move towards a common system and approach. The Spiez workshop has again demonstrated that it can create the necessary feedback and cross-talk between these different projects. A next opportunity to connect quality assurance exercises with the use of draft guidance documents and operating procedures, training, and practical tests will be the capstone exercise.

Whilst the early UNSGM workshops had a strong focus on the requirements for designated laboratories, much progress has now also been made on the interaction of investigators in the field and the laboratories that undertake the analysis of samples collected. This workshop discussed how these interactions can be facilitated by harmonising procedures, concepts and tools, to the extent possible. This may not necessarily lead to the adoption of prescriptive formal procedures such as standard operating procedures. Feedback from further practical exercises will help to find the right balance between standardisation / harmonisation and flexibility in order to accommodate the broad variety of possible scenarios and circumstances of a UNSGM investigation.

Certain technical issues also require further clarification, for example the issue of blanks, field testing and screening for mixed threats. Additional procedures or guidance documents may also have to be developed.

Broadening the geographical participation in the emerging UNSGM designated laboratories network remains a challenge. This will need effort and time, but it will be important that all Member States have trust in the system. Member States already engaged in this effort could encourage others, and concepts such as laboratory twinning may help attract interest in laboratories and countries that have not yet engaged with this initiative.

Within the concert of all the efforts to strengthen the UNSGM operational capacity and capability, the support and coordination of UNODA will be crucial to sustain interest and attract funding. As the work on the network broadens and efforts move gradually deeper into developing harmonised criteria, procedures, templates and other guidance, ensuring interoperability will also gain in importance.

Taken together, the workshop series offered by Switzerland and organised by Spiez Laboratory has again proven to be an effective and widely accepted platform for furthering the establishment of a trusted UNSGM bioanalytical laboratory network.