8th Meeting of the International Experts Group of Biosafety and Biosecurity Regulators: SARS-CoV-2

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Meeting Report: Lessons Learned by Established Biosafety and Biosecurity Regulatory Oversight Programs during the COVID-19 Pandemic

The COVID-19 pandemic continues to affect every corner of the globe more than a year after the World Health Organization declared a Public Health Emergency of International Concern. The pandemic provided a situation that tested the national biosafety and biosecurity oversight systems of the IEGBBR members. Despite pandemic planning and preparations undertaken well in advance of the current COVID-19 pandemic, an event of this scale and duration presented numerous challenges, even to the established oversight systems of IEGBBR member countries. During this virtual biennial meeting, IEGBBR members discussed challenges experienced by their regulatory programs and shared lessons learned during the pandemic. This report is being made available so that these lessons learned can be used to benefit biosafety and biosecurity oversight systems in the broader global community, towards increased global health security with respect to SARS-CoV-2 and other biological agents posing a public health risk.

Regulators largely relied upon available national regulatory tools during COVID-19 response. International tools are also available, such as the newly published 4th edition Laboratory Biosafety Manual of the World Health Organization, and guidance from The World Organisation for Animal Health describing considerations for veterinary labs to undertake human diagnostic SARS-CoV-2 testing. IEGBBR members were informed about biosafety and biosecurity tools in development including the consolidated repository of biosecurity and biosafety tools by Georgetown University and Global Affairs Canada, and the Biosafety Research Roadmap project to support the application of laboratory biological risk management and improve laboratory sustainability for low resource settings by Global Affairs Canada, the OIE, WHO and Chatham House.

The existing legislative biosafety and/or biosecurity frameworks in the IEGBBR countries were generally structured in a way that allowed effective public health response during the COVID-19 pandemic. There was consensus that regulatory oversight should not impede efforts necessary for public health service or response

Regulatory authorities are urged to take action now to leverage a level of attention during the COVID-19 pandemic never seen before, to prompt improvements to public health capacities and global health security.

during the COVID-19 pandemic, but at the same time would provide appropriate biosafety and biosecurity guidance and recommendations to allow the necessary work to proceed safely. There was also consensus among IEGBBR member countries in the classification of SARS-CoV-2 as an RG3 human pathogen. Areas where regulators experienced significant challenges included adapting the regulatory oversight programs to allow for pandemic response, handling of human clinical COVID-19 diagnostics, risk assessment and dual-use issues, risk group categorization, transport of specimens, the interface of human and animal pathogen oversight, identifying occupational exposure, and emerging technology.

1. Adapting Regulatory Oversight Programs

Regulatory challenges experienced during the pandemic prompted the development of a range of new tools in biosafety and biosecurity oversight. Many of the regulatory oversight programs of IEGBBR members have approval or notification processes for work with risk group 3 (RG3) biological agents, and these programs received very large increases in notifications or requests for approval. These were associated with laboratory work with the newly emerging SARS-CoV-2 virus or laboratories newly working with a risk group 3 agent, for example. In the interests of the response to the pandemic, most regulators fast-tracked the approval process for laboratory work associated with SARS-CoV-2. Another example was the repurposing of an existing sequence database originally used for the molecular surveillance, characterization, and further analysis of influenza isolates, being used for SARS-CoV-2 to allow for analysis of its diversity and evolution. Some regulatory regimes identified a need for increased regulatory flexibility in order to respond in a pandemic. In the context of a pandemic, the responsible pandemic pathogen might need a different regulatory oversight approach as compared to biological agents of comparable risk handled under routine circumstances, due to its widespread circulation within the community and the associated need for timely public health response. One example of regulatory flexibility was the temporary derogation from certain rules (e.g., notification, risk assessment, classification) associated with GMO legislation in the European Union to allow COVID-19 vaccines and treatments to be developed more quickly.

Most regulatory programs noted a large number of queries and new stakeholders that were not previously involved in biosafety and biosecurity. Providing regulatory biosafety information was a challenge as an increased number of stakeholders wanted information about safe diagnostic practices and personal protective equipment. These included laboratories working with the newly emerging SARS-CoV-2 virus, laboratories that had not previously worked with a RG3 agent, and new laboratories.

There is a need for continuity in biosafety and biosecurity oversight of laboratories during a pandemic, but this carries risk for regulatory staff that might be exposed to SARS-CoV-2 in the course of the travel and interactions necessary to carry out the associated work. To mitigate that risk while keeping regulatory staff available to mobilize as needed during the pandemic, some regulators prioritized COVID-19 vaccines for oversight staff and put in place quarantine and other pandemic measures.

It remains to be determined how the new tools and adaptations that have their origins in pandemic response will impact the regulatory oversight moving forward.

Remote or Virtual Laboratory Inspections

Several IEGBBR members adapted their programs to enable remote or virtual laboratory inspections to ensure compliance with the regulatory biosafety and biosecurity requirements and to replace portions of the on-site verifications to the extent possible. Review of documentation and verifications of procedural-

based items, for example, are aspects of inspection that can be completed without an on-site visit. Secure electronic systems are being used in the regulatory programs of some IEGBBR members to interact with stakeholders and more generally manage and modernize the regulatory programs. These same secure electronic systems can also be leveraged to allow staff to work remotely in the face of restrictions associated with the pandemic. Regulators note that a certain degree of physical inspection on-site is still required, for example in the case of new construction or verification of containment systems.

2. Handling of Diagnostic Specimens

Among IEGBBR member countries, there is a high number of laboratories working with SARS-CoV-2, and a high number of associated diagnostic specimens. A scheme of exemptions, exclusions, or temporary regulatory measures have been applied to the handling of human COVID-19 diagnostic specimens in most of the IEGBBR oversight systems during the pandemic. Some IEGBBR members do not capture SARS-CoV-2 under their regulatory oversight because the agent has not been added to the specified list of biological agents to be regulated. Regardless of the oversight approach, balancing the risks of the overwhelming surge of diagnostic specimens with regulatory burden and oversight was a noted regulatory challenge. Many of the regulatory programs handle COVID-19 surveillance wastewater samples similarly to diagnostic specimens. Some regulators have requirements for the importation of the virus or positive specimens.

The majority of diagnostic testing was undertaken under Biosafety Level 2 (BSL-2) or enhanced BSL-2 settings in most IEGBBR member countries. Even in cases where the handling of diagnostic specimens was exempt from oversight, guidance was elaborated for recommended biosafety practices to ensure that an appropriate level of biosafety would be maintained. In some cases, regulatory authorities communicated associated conditions for diagnostic labs, such as timeframes for the destruction of positive samples. Considerations for diagnostic specimens include having a risk assessment and risk mitigation plan in place, and timelines for storage after which specimens must be destroyed.

Diagnostic laboratories will also be testing non-COVID-19 clinical specimens that are handled in other (non-COVID-19) diagnostic streams during the pandemic, and in some of these, aerosols are not controlled. Biosafety practices or personal protective equipment may need consideration in these situations due to potential biosafety concerns arising in specimens originating from patients with COVID-19 that might unknowingly contain infectious virus particles.

Point-of-Care Testing

Point-of-care testing is a subset of diagnostic testing that occurs outside of laboratories. How to oversee such diagnostic testing outside of labs was a challenge to many regulatory oversight programs in terms of guidance, biosafety practices and personal protective equipment, staff resources and qualifications. Regulators provided guidance for biosafety practices and personal protective equipment for point-of-care testing. Recruitment of additional personnel necessitated providing training for biosafety practices and personal protective equipment, and in some countries defining qualifications.

Gaps and challenges in regulatory oversight represent opportunities for improvement.

3. Risk Assessment and Dual-Use

IEGBBR members employ a risk-based approach to risk assessment that considers the pathogen itself, the types of samples or specimens, and the activities to be undertaken. This aligns well with the new risk-based approach outlined in the WHO 4th edition Laboratory Biosafety Manual, and allows for flexibility of approach when circumstances change resulting in a need for reassessment. Many of the regulatory programs have expert groups or advisory committees that can be consulted regarding risk assessments and other biosafety-related areas; these have been consulted on various topics related to SARS-CoV-2.

In addition to the activities being performed, some regulatory programs considered the source or type of diagnostic specimens in order to assess biocontainment. For example, if the viral load is lower in blood specimens relative to nasopharyngeal swabs, or higher in wastewater samples originating from a geographic location known to have SARS-CoV-2 circulating, these factors could be considered and biocontainment assessed accordingly.

Options for additional biosafety practices for diagnostic specimens include specimen inactivation using validated protocols and the use of synthetic or inactivated positive controls. SARS-CoV-2 positive single strand RNA can be translated upon entry into a permissive cell and is therefore also considered infectious. Many regulators recommended biocontainment practices of BSL-2 for associated lab work. For some regulators, if there is no intention to introduce the RNA into a cell, BSL-1 is indicated, whereas BSL-3 is indicated if there is intention to introduce the RNA into a cell.

Regulatory programs assessed biocontainment required for new types of pandemic-related activities that had not previously been undertaken. One such activity involved the large scale growth of SARS-CoV-2 with subsequent inactivation for vaccine production. This was a new type of activity since previous activities related to vaccine production have used inactivated or attenuated RG3 agents. There were also clinical trials involving human challenge models for aerosolized RG3 SARS-CoV-2. Similarities to animal RG3 work and RG2 influenza human challenge models were weighed, and extensive consultation was necessary to determine associated biocontainment practices. Similarly, experiments involving the potential use of animals in COVID-19 diagnostics (e.g., detector dogs) would require consideration of biosafety for both the animals and humans, since SARS-CoV-2 is both a human and animal pathogen. Experiments involving genetic engineering also represent a challenge to risk assessment due to the need to take into account the likelihood and consequence of a gain of function or altered properties, and whether risk could be reduced to an acceptable level to allow work to proceed.

The increasing global circulation of SARS-CoV-2 variants of concern at the time of this meeting in March 2021 exemplifies one of the ways in which risk assessment will become complex as the pandemic proceeds. In addition to the wildtype or original SARS-CoV-2 strain, pathogen risk assessments also need to capture emerging variants that might have different characteristics, including transmissibility, pathogenicity, ability to evade diagnostics or vaccines, modified tropism or host range, etc. Regulatory authorities will need to consider the point at which separate risk assessments for the different strains or variants of SARS-CoV-2 will become necessary, as opposed to treating all of the strains and variants equally. One regulator noted a lesson learned was the need to actively sequence SARS-CoV-2 from specimens to determine the presence of variants circulating in the population that could carry increased virulence or transmissibility, in order to inform public health response. Consideration needs to be given to how all of these changing factors will impact risk assessments and how the regulatory regimes and containment requirements will be applied.

Among IEGBBR members' regulatory programs, risk assessments conducted for the purposes of biosafety and/or biosecurity often evaluate dual-use issues. Biosecurity and dual-use self-assessment tools for researchers and life science organizations are publicly available, with others in development. In cases where gain of function mutations are not subject to specific regulatory oversight measures, giving them consideration in other required biosafety and biosecurity risk assessments can inform risk mitigations. For SARS-CoV-2, dual-use issues could include gain-of-function mutations or a change in tropism or pathogenicity, for example. Some of the IEGBBR members' regulatory programs also evaluate risk mitigation plans for lab activities that have identified dual-use. Biocontainment practices for lab activities that could result in viral recombination may need special consideration.

4. Risk Group Categorization of SARS-CoV-2

All IEGBBR member countries are aligned in their classification of SARS-CoV-2 as an RG3 human pathogen, meaning that most activities involving culturing, also known as deliberate activities, would require BSL- 3 biocontainment. However, regulators are considering the factors and timing that might impact the continued RG3 categorization of the agent itself, given the continued widespread circulation of SARS-CoV-2 more than a year after the declaration of the pandemic. Factors that would need to be carefully weighed would include the following:

- Extent of circulation within populations
- Efficacy of vaccination
- Uptake of vaccination and extent of herd immunity
- Availability of therapeutics
- Possible future waves of disease caused by variants in a situation more like seasonal influenza
- Infection of animal species and the possibility of resulting mutation or recombination
- Impact of emerging variants

The national regulatory oversight systems under which SARS-CoV-2 is not currently captured will give consideration to a number of factors in deciding whether and when to include it. Notwithstanding, there is currently consensus that SARS-CoV-2 is an RG3 agent, and therefore associated biosafety measures and biocontainment should continue to be assessed accordingly.

5. Specimen Transportation, Imports and Transfers

The shipping of diagnostic specimens on such a large scale was a challenge as new personnel and companies began working in the area. The provision of additional training courses and materials in various formats were used to overcome this. Related challenges that were discussed include regulatory requirements for the importation of the virus or positive diagnostic specimens, and the role of oversight in domestic/internal transfers of potentially infectious materials. IEGBBR members gave consideration to the applicability of oversight to internal transfers of SARS-CoV-2, and whether it would apply at the level of the strain/variant or source (i.e. natural versus synthetic). However, with the limited available information at the time of the meeting, this consideration would need to be re-examined in the future. Regulatory authorities were also consulted in regards to appropriate transport methods for sending infectious laboratory waste for incineration when labs were faced with shortages of the routinely used supplies that allowed for its safe transport.

6. The Interface of Human and Animal Regulatory Oversight

The IEGBBR regulatory programs are aligned in categorizing SARS-CoV-2 as a RG3 human pathogen. However, the emergence of animal outbreaks resulted in reassessment of its animal pathogenicity as an RG2 animal pathogen, in addition to being an RG3 human pathogen. The dual human and animal regulatory oversight posed challenges for some regulatory programs. For example, differences in exemptions that were applied on the human side did not exist in the animal pathogen framework. The ways in which legislative frameworks for human and animal pathogens overlap or intersect may need to be reviewed from the perspective of flexibility and efficiency of adapting regulatory oversight in the context of public health response during a pandemic.

The intersection of human and animal biosafety and biosecurity is a recurring topic within the IEGBBR and is embodied by the One Health approach. The pandemic has proven that the assessment of risk of a pathogen can change over time, and this can impact both the human and animal components. In turn, the regulatory regimes themselves then also need to be adapted. As such, the broader inclusion of animal health regulatory partners in public health control and health security needs to be considered, as has been communicated prior to the pandemic by many public health security stakeholders.

7. Identifying Occupational Exposure

The regulatory biosafety and biosecurity oversight systems of IEGBBR member countries include reporting requirements for possible occupational exposures of lab workers to the biological agents with which they work. In the context of the widespread circulation of SARS-CoV-2 within communities during the pandemic, it could be challenging to differentiate these sources of exposure in the event of illness in a lab worker. Accordingly, regulatory programs should review their laboratory incident or laboratory worker illness reporting/monitoring systems. If faced with the possible occupational exposure of a lab worker resulting in illness, regulators can consider whether a workplace incident occurred that can be linked to disease, where something went wrong resulting in a possible occupational exposure. In the case of a lab-acquired infection, the involvement of local public health is a recommended means to assist with prevention of local spread. This would be particularly important if the associated lab is working with strains that are not circulating locally.

8. Emerging Technology

The oversight of biosafety and biosecurity faces two separate issues with respect to misuse in the life sciences - accidental misuse associated with legitimate activities and deliberate nefarious activities. The latter is much more challenging to oversee and tends to lie with law enforcement and intelligence communities. For the former, there is quite a range of regulatory and non-regulatory oversight approaches used among the regulatory programs, and this topic is being addressed in the IEGBBR's upcoming Review of Dual-Use project.

The COVID-19 pandemic has resulted in the potential for misuse in the life sciences to be featured in the media, with stories ranging from hypotheses about the origins of the virus through to potential bioweapons and biological warfare. However, in general, specific examples of potential misuse associated with SARS-CoV-2 are a cause for concern broadly, as opposed to being specific to SARS-CoV-2. For example, technology that can enable the creation of virus particles from RNA or DNA raises concerns about the oversight of purchases or transfers of certain RNA or DNA sequences. These concerns would apply to SARS-CoV-2 as well as to a range of other biological agents. Some regulatory programs consider

the intent to produce a biological agent similarly to culturing, thus such handling of RNA or DNA would also be covered. Some regulators are in the process of considering how to increase oversight of obtaining RNA or DNA sequences and the synthetic creation or recreation of viruses, and some regulators have encountered the recreation of viruses by labs.

The IEGBBR regulatory authorities discussed potential dual-use issues associated with synthesis companies and possible approaches for risk mitigation. One option is to put agreements in place outlining the screening of genetic material against pathogens, and these agreements may be linked to funding allocation. One goal would be for synthesis companies to develop a mechanism for identifying potential suspicious orders, whether based on the target or the client. Some regulators have begun outreach to synthesis companies.

The range of emerging technologies underscores the need for outreach to a broad range of stakeholders, including some that don't routinely engage with the biosafety and biosecurity authorities, such as funding bodies and journals. This can be particularly helpful when the stakeholder groups are national in scope. The use of real world examples has been found to be an effective strategy to reach life sciences researchers, who may otherwise find the subject matter not applicable to them.

9. Future Considerations

The future path of the COVID-19 pandemic remains an unknown. Will SARS-CoV-2 and its variants continue to circulate among the population? Regardless of the specifics, ongoing risk assessment will continue, and biosafety and biosecurity oversight will have to be adapted accordingly.

There is a large number of laboratories possessing and handling not only diagnostic specimens, but possibly also positive controls that might contain viable materials. Though all IEGBBR members have associated biosafety and biosecurity requirements that form a part of the system of established oversight, measures or practices for diagnostic specimens and positive controls may need to be re-evaluated in the future. This would affect a high number and a wide range of labs, including diagnostic and research labs. A range of specimen types would need to be given consideration, including wastewater and environmental samples. Such a scenario would have parallels to the polio eradication initiative and diagnostic specimens in labs after the Ebola outbreaks that may be applicable.

For the regulatory programs that do not currently oversee SARS-CoV-2 as well as those for which diagnostics are operating under exemptions and exclusions, there will be challenges associated with the storage and tracking of COVID-19 diagnostic specimens, particularly positive specimens. The regulatory programs in all IEGBBR member generally have labelling, storage and inventory requirements for RG3 agents that are verified during inspections, but practices for diagnostic specimens of the pandemic pathogen have different applicable measures in many of the IEGBBR member countries. In some IEGBBR member countries, labelling and tracking of samples falls under quality management systems. After the pandemic, regulatory programs may need to consider how to catalogue the SARS-CoV-2 viral cultures/strains/isolates held and stored in laboratories not otherwise captured by the regulatory oversight, as well as a strategy that outlines risk mitigation measures that can be taken to address associated biosafety and biosecurity concerns. A higher risk would be associated with forgotten or improperly tracked diagnostic samples, whereas retention in dedicated, reference, or research labs would be anticipated to be in compliance with regulatory oversight.

In IEGBBR member countries with list-based oversight, the regulatory oversight applies to agents specified on a list. Considerations during the pandemic for this type of oversight included how, whether and when to adjust inclusion for SARS-CoV-2, and other agents posing a public health risk, or whether alternative approaches to the oversight of pandemic pathogens would be warranted. A list-based system might also have limitations in terms of emerging variants of the virus.

IEGBBR members noted that biosecurity guidance could be enhanced for future versions of guidance provided to labs handling diagnostic or wastewater specimens that are otherwise exempt from regulatory guidance; however, this does depend to some extent on how the future path of the pandemic unfolds.

About the IEGBBR

Established in 2007, the IEGBBR coordinates and leads concurrent projects related to the international alignment, strengthening, and advancement of biosafety and biosecurity regulatory oversight systems. One of the goals of the IEGBBR is to strengthen international biosafety and biosecurity by sharing expertise and lessons learned from the perspectives of our established regulatory regimes with the global community.

The IEGBBR develops reference materials like this meeting report that are relevant to all countries, including developing countries and countries such as the IEGBBR members that already have established biosafety and biosecurity oversight frameworks. This is due to the universal nature of the IEGBBR's reference materials that can benefit the international community, regardless of level of development or resources.

For additional information, please consult the IEGBBR website. Click here to access the Google Play store for the IEGBBR's biosafety and biosecurity capacity-building mobile application, "IEGBBR Compendium of International Biosafety and Biosecurity Oversight Systems for Human and Animal Pathogens and Toxins".

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