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Preventing inadvertent laboratory release of pathogens:

Substantive elements for a WHO international agreement on pandemic prevention, preparedness and response

Discussion Note

Overall disclaimer:

This paper has been prepared by the services of the European Commission on the basis of initial internal discussions as well as in consultation with numerous experts. **The paper does not purport to be an exhaustive or comprehensive review of the complex issues covered therein.** It is only intended to contribute to the debate in the context of the deliberations of the Intergovernmental Negotiating Body (INB).

The paper should not be regarded in any way as a negotiating position. The paper and its content are entirely without prejudice to any future proposal. The illustrative provisions included in the paper are only aimed at exemplifying how provisions could look like. This does not imply that such provisions should be taken up for consideration in the upcoming negotiations.

The biosafety and biosecurity standards used by high-containment laboratories[1] handling the most dangerous pathogens and biological agents remains a matter of concern. Even countries with a high level of technical capacities and resources are not immune from risks of leaks and other unforeseeable events with potentially dire consequences nationally and internationally. The negotiation of an international agreement on pandemic prevention, preparedness and response ("pandemic agreement", PA) offers the possibility of enhancing international cooperation in this field.

This paper aims to further develop the elements included in section 1.c) of the EU contribution made to the INB on 29 April 2022 (see Annex) and further feed the reflection on the challenges related to the prevention and control of public health threats with pandemic potential.

I. Justification for inclusion in the pandemic agreement

Handling pathogens that represent a significant potential threat for human and animal health, and for the environment, can be risky when the appropriate biosafety and biosecurity measures and standards are not in place and/or not complied with.

[1] "Laboratories using maximum containment measures, which have previously been described as biosafety level 4 (BSL4/P4) containment laboratories, are those that offer the highest level of protection to laboratory personnel, the community and the environment. There are few such laboratories in the world as they are very expensive to build, operate and maintain, and are not required for most work. Normally, such laboratories must comply with highly detailed national legislation and guidance, even before being given permission to operate, and they may be subject to numerous regulatory inspections on a regular basis." See WHO, Laboratory biosafety manual, fourth edition, 2020, at page 59.

These concerns and risks play out against the background of few agreed global standards on biosafety and biosecurity of laboratories handling human, animal[2] and plant pathogens. There is also no internationally agreed, comprehensive and effective framework for inspection and verification of the biosafety and biosecurity standards and conditions.[3]

In relation to security issues, inspections of industrial or scientific facilities are more common in the arms control and disarmament field, in particular:

1) under the system of safeguards of peaceful uses of nuclear materials managed by the International Atomic Energy Agency notably under the Treaty on the Non-Proliferation of Nuclear Weapons.

2) under the international regime of prohibition of chemical weapons based on the Chemical Weapons Convention and the Organization for the Prohibition of Chemical Weapons (OPCW). However, there is no equivalent system of inspections under the 1972 Biological Weapons Convention as there is no verification regime attached to the Convention. Nevertheless, there are confidence building measures declarations submitted annually on a voluntary basis.

In relation to safety issues, the Convention on Nuclear Safety and the Joint Convention on the Safety of Spent Fuel Management and on the Safety of Radioactive Waste Management, concluded under the auspices of the IAEA, provide a useful example of what has been achieved at the international level with the recognition that it was in the Parties common interest to achieve high levels of safety in the fields cover by these Conventions. Both requires State Parties to submit reports on the implementation of their obligations for "peer review" at meetings that are held every three years. The IAEA has also issued codes of conduct and other guidance material on the safety of nuclear installations and materials, but to our knowledge its inspection functions are not dedicated to verifying compliance with those standards.

The international concern around the safety and security of biological laboratories, the high level of risk in case of admittedly infrequent incidents, and the importance of building trust in this area militate in favour of discussing the inclusion of this topic in the future instrument on pandemic preparedness and response. Such instrument can provide an effective framework to foster the mutual confidence, cooperation and accountability required to address this complex issue. It can also provide the basis for the adoption of scientifically sound and politically acceptable common reference standards, as well as the designation of one or a group of international organisations to oversee the implementation of the agreed rules and support parties in this respect. The integrity of a legal framework of this nature would benefit from a carefully devised system of periodic inspections of the laboratories concerned in order to verify the application of agreed standards, identifying problems requiring international assistance, and build mutual trust. In view of the nature of the exercise and WHO's experience on the repositories of variola virus, the latter could be entrusted with the primary responsibility of overseeing the implementation of the agreed framework as regards human pathogens. Given the joint role of the Food and Agriculture Organization of the United Nations (FAO) and the

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[2] International standards on biosafety and biosecurity of laboratories handling animal pathogens have been adopted by the World Organisation for Animal Health (WOAH, https://www.woah.org/en/what-we-do/standards/codes-and-manuals/terrestrial-manual-online-access/).

[3] There is for certain animal diseases such as rinderpest (joint FAO/WOAH post-eradication strategy, incl. inspection and approval of RPV holding facilities, see https://www.woah.org/en/disease/rinderpest/#ui-id-3 and https://www.fao.org/ag/againfo/programmes/en/rinderpest/home.html). Likewise, the poliovirus-specific Biorisk Management Standard, included under the WHO Global Action Plan for Poliovirus Containment (GAPIV), provides a framework for national facilities certification and WHO verification. (see WHO-Global-Action-Plan-for-Poliovirus-Containment-GAPIV.pdf (polioeradication.org).

World Organisation for Animal Health (WOAH) in the implementation of rinderpest post-eradication, those organisations should continue to be entrusted jointly with the primary responsibility of overseeing the implementation of the agreed international framework as regards animal pathogens.

Given that pathogens can evolve (animal pathogens becoming human pathogens and vice versa) and have significant implications for biodiversity, it will be appropriate for WHO, FAO WOAH and UNEP to work closely together on the implementation of the new framework for laboratory safety and security, building on the work already undertaken. Appropriate regional entities could be also associated to this work.

The adoption of generally applicable international rules or guidelines to ensure the biosafety and biosecurity of all laboratories storing and using dangerous pathogens would be a major step forward towards the prevention of accidental leaks with potentially dire consequences, and of intentional release of biohazards by an individual. It would harmonize and render more transparent scientific practices, build confidence, facilitate cooperation as well as mutual learning.[4]

II. Relations with applicable WHO norms or policies, as well as IHR (2005), and other international standards and instruments

The IHR does not cover the regulatory requirements for biosafety and biosecurity per se. However, these are covered in the Joint External Evaluations and the WHO IHR benchmarks.

The WHO has provided laboratory biosafety and biosecurity guidelines for many years and has recently published the fourth edition of the WHO Laboratory Biosafety Manual (LBM), which provides a voluntary global standard setting out best practices in biosafety. As a result, there are several documents laying down laboratory biosecurity and biosafety standards. The level of actual use and verification remains patchy.

The WHO secretariat carries out biennial inspections of the two authorized repositories for variola virus (in the Russian Federation and the United States, respectively) as requested in the following terms by WHA resolution WHA60.1 (2007):

> *…. to maintain biennial inspections of the two authorized repositories in order to ensure that conditions of storage of the virus and of research conducted in the laboratories meet the highest requirements for biosafety and biosecurity; inspection mission-reports should be available for public information after appropriate scientific and security redaction;* (emphasis added)

The inspections are carried out in full cooperation with the personnel of the repository concerned and the team often includes representatives from the other repository. Inspecting teams visit the two authorized repositories for variola virus every two years.[5]

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[4] It may also facilitates compliance with international non-proliferation regulations such as United Nation Security Council Resolution 1540 regulations and the Biological and Toxin Weapons Convention (BWC).

[5] The inspection reports are published on the WHO web site at: https://www.who.int/activities/variola-virus-repository-safety-inspections. They cover and comment on the following topics, including on improvements and challenges with regard to the outcome of the previous inspection:

1) Biological risk management system;
2) Risk assessment;
3) Pathogen and toxin inventory and information systems;
4) General safety;
5) Personnel and competence;

The WHO Global Action Plan for Poliovirus Containment (GAPIV) establishes a biorisk management standard with inspection schemes.

The WHO Lyon Office has developed global guidance documents and tools and conducts training activities to support countries on laboratory and biosafety strengthening. The Office has developed the Global Laboratory Leadership Programme (GLLP) and the Laboratory Quality Management Training to provide current and future laboratory leaders the knowledge and skills needed to play their role regarding laboratory biosafety and the detection, prevention and control of diseases.

In the veterinary field the WOAH Manual of Diagnostic Tests and Vaccines do include those international standards[6]. In addition, the WOAH has renowned collaborating centres specialized in this area that contributes to implement these standards worldwide.[7]

Rinderpest (RP) was declared eradicated by the WOAH World Assembly and by the FAO Conference in 2011. Since then, both organisations have been mandated by their membership to jointly implement a global post-eradication strategy to maintain global RP freedom. This includes destruction and sequestration of RPV stocks, which led to a significant reduction in number of countries and laboratories maintaining RPV containing material to a minimum number of FAO/WOAH approved high-containment laboratories ("RPV holding facilities", approved either for storing rinderpest virus containing material, or for storing manufactured vaccines and vaccine stocks). A comprehensive system has been put in place through a FAO-OIE Rinderpest Joint Advisory Committee (JAC) to develop procedures and technical standards for the approval and verification of those facilities (including regular inspections), as well as to approve RP research projects in those facilities.

The European Commission for the Control of Foot-and-Mouth Disease (EuFMD), a FAO Article XIV body with 39 member States, has elaborated Minimum Biorisk Management Standards for FMD Laboratories that are binding for EuFMD member States (including all EU MSs).[8] Those standards were developed for the first time in 1985 and updated several times afterwards.

At EU level, the Animal Health Law (Regulation (EC) 2016/429, applicable since 21 April 2021), in its art. 16, requires laboratories and other entities handling disease agents to apply adequate biosafety and biosecurity measures. It also empowers the Commission to develop

6) Good microbiological practices (GMP);
7) Clothing and personal protective equipment;
8) Human factors;
9) Healthcare;
10) Emergency response and contingency planning;
11) Accident and incident investigation;
12) Facility physical requirements;
13) Equipment and maintenance;
14) Decontamination, disinfection and sterilization;
15) Transport procedures;
16) Security.

6 See chapters 1.1.4 and 2.1.3 + other on vaccines - Terrestrial Manual Online Access - WOAH - World Organisation for Animal Health).

7 See Global Chemical and Biological Security – Sandia National Laboratories + report_368_2021_Laboratory_Biorisk_Management_UNITED_STATES_OF_AMERICA.pdf (woah.org) .

8 Special Committee on Biorisk Management (SCBRM) | The European Commission for the Control of Foot-and-Mouth Disease (EuFMD) | Food and Agriculture Organization of the United Nations (fao.org).

those measures in a delegated act, which will include the responsibility for the Commission to verify compliance with them through its controls in Member States (act still to be developed).

It is also important to note that there are a series of voluntary standards, which can be drown upon, such as ISO/IEC 17025:2005 with general requirements, ISO 15189:2007 dedicated to medical laboratories and more particularly ISO 35001:2019 on biorisk management.[9]

International biosafety and biosecurity related provisions included in the future pandemic agreement should draw on the experience matured by the WHO since 2009, and by FAO and WOAH since 2011.

As noted above, safety and security standards are issued by the IAEA with regard to nuclear installations, facilities and materials, and both the IAEA and the OPCW carry out inspections to verify compliance with obligations to prevent the development of nuclear and chemical weapons, respectively. The subject matter and the object and purpose of those regimes are very different from the biosafety and biosecurity of laboratories handling dangerous pathogens. However, the WHO, FAO, WOAH and UNEP secretariats (as possible secretariats of the PA in this area) could draw to some extent from the experiences matured under those regimes and by those institutions in terms of processes to develop the relevant universal standards as well as with regard to good inspection practices.

III. Possible provisions in the Pandemic Agreement

Without prejudice to further reflection and discussion within the INB and solely by way of examples, the pandemic agreement, including by way of voluntary guidelines or subsequent protocols, could follow the approach and contain the types of measures set out below:

1. It may be limited to laboratory biosafety and biosecurity considerations;
2. It may be limited to specific groups of pathogens, to those with particular characteristics or to specific types of laboratories, e.g. those involved in 'gain of function' experiments, in order to avoid over-inclusiveness;
3. It should take account of existing frameworks;
4. It should be applied to biological laboratories, whether public or private, declared periodically by each party;
5. The Conference of the Parties would adopt and periodically update biosafety and biosecurity standards developed by experts convened with the support of WHO, FAO, WOAH and UNEP, while taking into account existing relevant standards;
6. Parties would report periodically on the application of the agreed standards and problems encountered. One promising approach would be for Parties to agree on voluntary standards.[10] While these would not be legally binding per se, Parties would have to justify significant departure from them;
7. WHO, FAO and WOAH would provide support to Parties, including through periodic visits to promote the application of the agreed standards, and report to the Conference of the Parties. The timing of the inspections and the composition of the team would be agreed in advance with the Party concerned;

[9] ISO, General Requirements for the Competence of Testing and Calibration Laboratories, ISO/IEC 17025:2005; ISO, Medical Laboratories: Particular Requirements for Quality and Competence, ISO 15189:2007; ISO, Biorisk management for laboratories and other related organisations, ISO 35001:2019.

[10] These will need to be consistent with any international obligations the Parties may have already undertaken.

8. WHO, FAO, WOAH and UNEP would be responsible for providing or facilitating, at the request of the Parties concerned, technical assistance and capacity building, including through the activities of the WHO Lyon Office.

The provisions below are offered in order to start a concrete discussion with partners and stakeholders.

Article A (Biosecurity and Biosafety Standards)

The Conference of the Parties shall:

1) *Decide the information to be submitted by each Party with regard to the laboratories or other similar institutions to which the provisions of this section apply, including the biosafety and biosecurity measures applied at each laboratories and the security level attributed to it; the list of laboratories or other similar institutions submitted by each Party should be periodically revised;*

2) *Specify the groups of pathogens and biological agents and the type of laboratories requiring the application of the biosafety and biosecurity standards adopted pursuant to this Article;*

3) *Adopt and revise, as appropriate and while taking into account relevant international regulations, guidelines and standards, necessary minimum biosafety and biosecurity standards to be applied by each Party to the pathogens specified in this Article related to storage, handling, experimentation, transport, both within the jurisdiction of the Party as well as to another Party, and destruction.*

The standards referred to in subparagraph 3) above shall be elaborated drawing upon best practices developed by Parties as well as relevant international and scientific organizations, having particular regard to their resource implications and the limitations they may impose on the activities carried out in the laboratories concerned.

Article B (Reporting by Parties)

1. *Each Party shall report to the Secretariat[11] at intervals to be decided by the Conference of the Parties on its application of the standards referred in Article A (Biosecurity and Biosafety Standards), paragraph 2, the reasons for any significant deviation, from them as well as challenges and problems encountered in their application.*

2. *The Secretariat shall submit a summary report to the Conference of the Parties, reflecting in particular progress and challenges encountered by Parties in securing increasingly higher levels of biosafety and biosecurity.*

3. *Each Party shall report immediately to the Secretariat accidents within the laboratories listed under Article A (Biosecurity and Biosafety Standards), paragraph 1 with regard to the pathogens referred to in Article A (Biosecurity and Biosafety Standards), paragraph 2 that have resulted or may result in the release of those pathogens in the environment and may pose a risk to health. The Secretariat shall immediately inform the other Parties and offer or facilitate the provision of technical assistance to the Party or Parties concerned.*

[11] The institutional provisions of the PA will determine the arrangements to ensure the Secretariat functions. The WHO could provide Secretariat support to the PA. Different arrangements involving joint secretariat functions bringing together different international organisations, especially the Quadripartite organizations could be also envisaged in specific policy areas, especially when linked to One Health.

The Secretariat shall report to the Conference of the Parties about any such accident.

Article C (Implementation support)

The Secretariat shall periodically visit the laboratories listed under Article A (Biosecurity and Biosafety Standards), paragraph 1 for the purpose of supporting the Parties in the effective implementation of the biosafety and biosecurity standards adopted by the Conference of the Parties and of recommending possible improvements in the application of such standards. The conditions and modalities for carrying out visits under this Article shall be decided by the Conference of the Parties. The specific timing of such visits and the composition of the visiting team will be agreed upon with the Party concerned in accordance with such conditions and modalities.

Article D (Technical Assistance)

The Secretariat shall provide, or facilitate the provision of, technical assistance upon the request of any Party in order to assess and improve the biosafety and biosecurity features of any laboratory and other similar institutions. Parties shall collaborate with each other for the same purpose.

Annex: Excerpts from section 1.c) of the European Union contribution to the identification of the substantive elements for a convention, agreement or other international instrument on pandemic prevention, preparedness and response, as submitted to the INB on 29 April 2022

1. Preventing and controlling public health threats with pandemic potential

(…)

c) Preventing inadvertent laboratory release of pathogens through:

25. Elaborating and implementing biosafety regulations to control access to highly dangerous pathogens (including by considering promoting the global database registration of highly dangerous microorganisms used in research laboratories) and prevent their inadvertent laboratory release and providing inspection and training.

26. Enhancing the independent oversight of laboratory conditions and safety protocols to ensure biosecurity and biosafety.