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Report of the World Health Organization (WHO) Biosafety Inspection Team of the Variola Virus Maximum Containment Laboratories to the Centers for Disease Control and Prevention (CDC), Atlanta, Georgia, United States of America, 20-24 May 2019

World Health Organization

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EXECUTIVE SUMMARY

The World Health Organization (WHO) team of international experts carried out a biosafety and biosecurity inspection at one of the two WHO authorized variola virus (causative agent of smallpox) repositories: CDC*, in May 2019 in accordance with World Health Assembly resolution WHA60.1 (2007). [*the Centers for Disease Control and Prevention in the United States of America].

The activities of the WHO inspection team included inspection of the physical maximum containment facilities, the supporting engineering systems and the long-term secure specimen storage arrangement and the isolation hospital. Before entry into the maximum containment facility, the inspection team performed a detailed review of the recent decontamination process. The inspection team had interactive discussions with CDC staff, requested and reviewed instruction manuals, standard operating procedures (SOPs) and other relevant biological risk management documents.

Management and staff at CDC described their institutional commitment to biosafety and biosecurity by delivering detailed presentations of their facility systems and operations throughout the inspection. The team presented and discussed with CDC their findings of the inspection.

Since the last inspection in 2017, CDC has made significant improvements with many previous findings addressed and closed. The inspection team delivered a presentation at the end of the meeting related to the status of the various findings. The inspection team did not note any new findings requiring immediate corrective action (Priority 3) during the 2019 WHO inspection, although they have requested further work on some issues.

In conclusion, the CDC repository was found to meet international levels of biosafety and biosecurity for variola virus research and storage. This inspection report places no responsibility on WHO. Continued safe, secure storage and conduct of work with live variola virus remains the responsibility of CDC. The WHO requests CDC to submit an action plan to address the issues noted here for further improvement within 30 days of receiving this report.

CONTEXT

1. There are two authorized repositories of variola virus, namely, the Centers for Disease Control and Prevention (CDC) in the United States of America and FSRI SRCVB "VECTOR", Rospotrebnadzor in the Russian Federation. The World Health Assembly resolution WHA60.1 (2007) requests that the WHO maintain inspections of the two laboratories biennially in order to ensure that the conditions of storage of variola virus and research conducted in the laboratories meet the highest requirements for biosafety and biosecurity. In addition, in accordance with resolution WHA60.1, inspection mission reports should be available for public information following appropriate scientific and security redaction.

2. Dates for inspection of both repositories are coordinated with the decontamination of the maximum containment facility followed by the annual maintenance of the facilities. This allows the inspectors to enter areas of the facilities that are difficult to access during the handling of live variola virus. The WHO inspection team, consisting of international experts in a range of fields, visited CDC from the 20th to the 24th of May 2019 to meet the biennial inspection requirement of resolution WHA60.1. On the 19th of May, the designated inspectors met for a pre-inspection consultation to review the agenda, inspection practices and inspection protocol.

3. Two representatives of the other repository participated in the inspection as observers, excluding closed discussions among the WHO inspection team and during delivery of the results and recommendations to the inspected repository. This is sharing best practices as well as to ensure parity and impartiality of the inspection.

INSPECTION PROGRAMME

4. By agreement with both repositories, the present inspection included the elements defined in the protocol used in the 2009, 2012, 2015 and 2017 inspections. The European Committee for Standardization (CEN) Workshop Agreement (CWA) 15793 (2011) was used exclusively to structure the inspection and to follow up previous "findings". The facilities were not assessed for conformity to the CWA.

5. The inspection team and repository representatives agreed to use a transparent rating scale to categorize the findings at the two repositories. To ensure clarity and a consistent approach, findings are categorized as follows:

- Observations are either positive remarks, including examples of robust controls or other best practices, or related issues that are not directly associated with biosafety and biosecurity.
- Priority 1 findings indicate that an improvement is advisable.
- Priority 2 findings indicate that a timely remedial measure is required.
- Priority 3 findings indicate that immediate corrective action is required.

6. Previous findings found to be ongoing at the next inspection will contribute to the prioritization of future findings and issues to be addressed in any subsequent action plans.

7. The inspection took place over five days and included a full one-day inspection of the physical maximum containment facility designated for research with variola virus, its

supporting mechanical systems such as the Heating Ventilation and Air Conditioning (HVAC), the effluent decontamination systems and the gamma cell irradiator. All inspection team members were permitted to enter the restricted-access, long-term variola virus specimen storage area. The inspection team also visited half a day the isolation hospital including the ventilation floor.

8. The WHO inspection team heard presentations from and held interactive discussions with CDC staff. The team specifically requested records, regulatory instruments, institutional rules, instruction manuals and meeting minutes as necessary for detailed review. The inspection team viewed manuals, layout of the facility, policies and explanations of the hierarchy of documents. The final day provided an opportunity to discuss and confirm the WHO inspection team's understanding, observations and recommendations, which the inspection team presented to CDC.

9. The WHO inspection team made every effort to assess the facility, documents and current practices over a limited timeframe. As the facility was not operational due to scheduled maintenance, the team did not observe any actual practical work during the inspection. The inspection team appreciated the collaborative attitude and committed engagement of the CDC management and all responsible staff throughout the inspection. Presented below are the results of the WHO inspection, the aim of which is to reduce risk and encourage further use of international best practices.

1. Biological risk management system

10. CDC representatives presented the organisational hierarchy and provided documentation of the policies, processes and procedures supporting their biological risk management (BRM) system within the facility. The inspection team reviewed the institutional codes of practice including oversight boards and committees. The team also examined responsibilities and accountability for biological risk management through a variety of manuals, committee meeting minutes and other relevant documents.

11. The inspection team did not have any concerns relating to the biological risk management system.

2. Risk assessment

12. CDC explained that the development of the biological risk management program is ongoing, including developing risk management systems for programs which support the laboratory's variola virus research. The inspection team was shown several risk assessments for example one for experiments with mice and another one for the effluent decontamination system.

13. The previous inspection report noted the ongoing finding (Paragraph 15): *"…biological risk management issues are still not reviewed consistently in all CDC programmes, although*

the process is being developed. As information from other programmes could contribute to improving risk elements in the variola programme, a systematic approach is advisable…it should be extended to include facility and maintenance processes in order to determine where tight controls on facilities and equipment are required…" The process for risk assessment is in place including SOPs for laboratory equipment. The risk assessment is now controlled through a structured governance process. There is evidence that CDC are making positive steps to implement a maintenance programme.

However, as this is still in development, the finding therefore remains open.

14. *Priority 1 Finding*: The process of risk assessment should be implemented for maintenance, including failure scenarios for all safety critical systems. Examples include failures of Effluent Decontamination System (EDS) and fan systems. The process and the documentation should be in line with the already implemented Quality Management System (ISO 17025).

3. Pathogen and toxin inventory and information

15. The inspection team examined the working stock and long-term storage areas for variola virus and viral DNA as well as the specimen packaging used for storage of vault stocks, repository stocks and working stocks. The process for recording and inventorying working and archival collections is well controlled which includes a restricted access electronic database system with an automated audit trail. In September 2018, the repository's sealed boxes containing variola virus stocks had been temporarily moved to gasket-sealed containers in a minus 80°C freezer within the same High Containment Laboratory because of a failure of the liquid nitrogen freezer. CDC formally reported accessing the repository to WHO at the time of moving the stocks.

16. The inspection team did not have any concerns relating to pathogen and toxin inventory and information.

4. General safety

17. The inspection team reviewed aspects on general safety throughout the visit and did not have any concerns relating to general safety.

5. Personnel and competence

18. CDC staff explained that a standardized training form was adopted by the Poxvirus and Rabies Branch to comply with CDC's Quality Management System. The inspection team had an opportunity to watch a training video which included for example the use of containment

suits and associated PPE, daily safety checklist, use of chemical showers, transfer of agents, waste management procedures, noise protection, emergency procedures and spill clean-up.

19. *Observation*: A decommissioned laboratory was converted to a new containment laboratory training facility to train CDC staff in laboratory procedures such as testing and use of new laboratory decontamination equipment and emergency drills. Planned training and training videos represent best practices.

20. *Priority 1 Finding:* Succession planning was explained for the maximum containment laboratories manager, including the deputy manager's role, in relation to the applicable human resource policies. The inspection team recommends consideration of assigning deputies for all critical positions.

21. Previous finding (paragraph 23): *"Inconsistencies were found in the training records reviewed with respect to signatures and dates. Therefore, a more standardized process is required for all aspects of the required training, including at higher institutional levels".* The training documentation is designed to be compliant with ISO17025 and has been adopted into the document control system in place within the Poxvirus and Rabies Branch. This finding is now closed.

6. Good microbiological practices and procedures

22. The variola virus stocks are stored within liquid nitrogen tanks safely above the liquid nitrogen level in the vapor phase. The samples are securely sealed in primary containers that are stored within secondary containers that are sealed with tamper evident seals.

23. The inspection team did not have any concerns relating to good microbiological practices and procedures.

7. Clothing and personal protective equipment

24. The previous report recommended a review of the taping procedure for the glove-suit junction and for suit tear repair. CDC explained the procedures for suit repair and the new taping procedure during the visit of the inspection team. The SOPs had been updated accordingly.

25. The inspection team did not have any concerns relating to clothing and personal protective equipment.

8. Human factors

26. The inspection team had discussions with CDC on this element and the team did not have any concerns relating to human factors.

27. The inspection team did not have any concerns relating to human factors.

9. Healthcare

28. The isolation ward in the contracted hospital was visited by the inspection team. The patient rooms and the attached laboratory as well as the autoclave and the ventilation deck were inspected. The SOPs for waste treatment and entry and exit from the patient suite were reviewed.

29. Previous finding (paragraph 35): *"As* variola virus *is environmentally more stable than Ebola virus, the inspection team recommends a review of: 1) the decontamination protocol for the patient room at the end of treatment (e.g. soft furnishings); 2) the suitability and robustness of secondary barriers in place in the clinical laboratory; and 3) whether the isolation units provide sufficient biocontainment for airborne transmitted infectious diseases".*

1) Although the inspection team did not have the chance to review the SOP regarding decontamination, procedures were explained during the site visit. The team observed that items previously noted as concerns with the decontamination were addressed, soft furnishing have been removed, porous ceiling tiles replaced and closet door with room exhaust removed. The inspection team considers the room as suitable for gaseous decontamination.

2) The inspection team was shown the new clinical laboratory including the anteroom.

3) To contain airborne transmissible diseases in the isolation units, there is a pressure cascade from the hospital floor to the anteroom of the patient room to the patient room to prevent airflow from the patient room. The exhaust air from the patient room is HEPA filtered before released.

Improved procedures were explained to the inspection team. As such, this previous finding is now closed.

30. Previous finding (paragraph 36): "*Flows of work and equipment used are important in terms of effective biosafety. The inspection team recommend a review of:*