Report of the World Health Organization (WHO) Biosafety and Biosecurity Inspection Team of the Variola Virus Maximum Containment Laboratories to the Centers for Disease Control and Prevention (CDC),

Atlanta, Georgia, United States of America, 2-6 May 2022
EXECUTIVE SUMMARY

The 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 2022 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 2019, CDC along with its designated health care facility 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 2022 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 the 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 2nd to the 6th of May 2022 to meet the biennial inspection requirement of resolution WHA60.1. On the 1st 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 ordinarily participate 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. Unfortunately, due to current circumstances, two representatives of the other repository were unable to participate in the inspection this time.

INSPECTION PROGRAMME

4. By agreement with both repositories, the present inspection included the elements defined in the protocol used in the 2009, 2012, 2015, 2017, and 2019 inspections. The European Committee for Standardization (CEN) Workshop Agreement (CWA) 15793 (2011), which was then transformed to International Organization for Standardization (ISO) 35001:2019, was used exclusively to structure the inspection and to follow up previous “findings”. The facilities were not assessed for conformity to the CWA or the ISO standard.

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 breathing air supply and life support systems. The inspection team members were permitted to enter the restricted-access, long-term variola virus specimen storage area. The inspection team also spent half a day visiting the isolation hospital.

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, but had the possibility to watch a training video. 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 overviewed 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. Observation: The biological risk management system at CDC is complex with many teams involved. Documentation of the risk management system was useful to enable understanding by the inspection team.

12. Observation: The High Containment Laboratory (HCL) Operations Group (HOG) is very proactive and beneficial for the facilitation and improvement of the HCL facilities. The inspection team suggests adding specific list of actions into the discussion and meeting minutes. Such actions can then be reviewed, updated or closed out at subsequent meetings and these should also be noted in the minutes.
2. Risk assessment

13. CDC explained that the development of the newly revised biological risk management program including developing risk-based management systems for programs supporting the laboratory’s variola research is ongoing. The inspection team was shown several risk assessments such as the effluent decontamination system and research experiments including those involving humanized mice.

14. The previous inspection report noted the ongoing finding (Paragraph 13): “...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.” The finding remained open as the implementation of a maintenance programme was still under development.”. CDC is taking a proactive approach and developing a new risk assessment and management approach. Their implementation of a suitable maintenance programme allows for the closure of this finding.

15. Previous finding (paragraph 14): “The process of risk assessment should be implemented for maintenance and to include failure scenarios for all safety critical systems. Examples include failures of Effluent Decontamination System (EDS) and fan system. The process and the documentation should be in line with the already implemented Quality Management System (ISO 17025).” CDC has performed risk assessments on critical support systems and addressed failure scenarios most likely to occur for each system. The inspection team reviewed risk assessments for breathing apparatus, Effluent Decontamination System, and Air System Supply and Exhaust. This finding is now closed.

16. Priority 1 finding: There needs to be a more structured approach to risk assessment including, but not limited to for example:
   • A standardised approach to risk assessment training of personnel
   • A standardised template
   • Clear distinction between hazards and risks
   • Identification of risk level
   • Clear sign-off process to ensure understanding, acceptance and accountability by those performing the work
   • Version control
   • Standardised review process whereby risk assessments are not only reviewed by appropriate individuals, but are also re-read and signed off including date by those performing the work.

The new risk assessment process being developed should include these elements.

17. Observation: Some risk assessment documents stipulate to “see relevant documents”. Specific documents should be identified to avoid misinterpretation e.g. refer to documents x, y, z.
3. **Pathogen and toxin inventory and information**

18. The inspection team examined the working stock and long-term storage areas for variola virus and viral DNA. 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.

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

4. **General safety**

20. 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**

21. A dedicated training facility was set up in its place and is now ready for use. A training video on entry and exit of the BSL4 lab including emergency scenarios was viewed by the inspection team. Practical scenario-based exercises have also been undertaken to test emergency procedures, which had led to continual improvement. Further exercises are planned.

22. Previous finding (paragraph 20): “Succession planning and deputy's role were explained for the maximum containment laboratories manager in relation to the government rules. The inspection team recommends to consider assigning deputies for all critical positions.” A dedicated HCL engineer was hired. The inspection team was shown a list of back-up support positions for some critical positions, but not all. Finding remains open.

6. **Good microbiological practices and procedures**

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

7. **Clothing and personal protective equipment**

24. The inspection team visited the changing room of the high containment facility and were shown the procedures for checking PPE prior to donning including filling in of the PPE check logbook. The inspection team were also shown a filmed example of the process for sample removal from an LN₂ tank within the facility.

25. **Priority 1 finding:** The logbook for pre-donning suit checks seems to be a little misleading and unclear in terms of what information is required. The logbook is
inconsistently and not always completely filled in. This inspection team suggests a review of the logbook including adding an additional note to state the longevity of the suits.


8. Human factors

27. Observation: The inspection team noted that there were significant reliance and pressures on a few core members of staff. As such, systems for reducing the burden, for instance an on call schedule using deputies should be considered.

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.

29. Previous finding (paragraph 31): “The inspection team raised concerns and recommends a thorough assessment of the engineering controls and its validation such as autoclave, HEPA filter, placement of roof exhaust and locations of the air inlets and outlets of the isolation rooms and the laboratory as well as the procedures related to handling potentially infectious patients specifically smallpox.” The inspection team was impressed with evidence-based decision making and efforts made to improve safety at the contracted hospital. Its much-improved approach for waste handling and risk mitigation had been considered with extensive validation of the autoclave system having been completed. The inspection team saw the roof exhaust, which had been extended to minimise the possibility of re-entrainment. Locations of inlets and outlets for patient rooms had been relocated to enable better airflow. The new laboratory for patient management was well laid out with good workflow. This finding is now closed.

30. Priority 1 finding: a) Air inlet and extract vents are too close together in the lab, suggest validation of air mixing and possible relocation to opposite ends of the longest section of the lab. b) The inspection team suggests the performance of a risk assessment and evidence-based validation for the treatment of the toilet to ensure the toilet bowl and any solid stool are disinfected. This should also be carried out for the use and disinfection of the shower and shower effluent.

10. Emergency response and contingency planning

31. The previous report recommended to include in the next emergency training a scenario of an unconscious worker alone in the lab. The CDC had conducted exercises for an unconscious worker alone in the laboratory. These exercises have been written up for the inspection team.
32. **Observation:** Continue with relevant emergency response exercises for continual refreshing of emergency procedures and include for instance the need for cardiopulmonary resuscitation (CPR) within the high containment laboratory and a Security Operations Centre (SOC) response to lone worker collapse.

**11. Accident and incident investigation**

33. The inspection team was walked through the electronic incident reporting management software system currently in place, which works well. Incidents including near misses are reported through Cority whereby details of the incident and action taken to reduce the likelihood of future incidents are recorded. This highlights good practice and the inspection team did not have any concerns relating to accident and incident investigation.

**12. Facility physical requirements**

34. The inspection team was informed of a new high containment laboratory facility being planned. The new facility is in the last stages of planning with a view to the build being completed within the next 6-8 years. The inspection team were taken through a virtual reality tour of the new facility. The inspectors encourage end user involvement throughout the development of the new facility to ensure the most appropriate and practical set-up is achieved.

35. The previous report recommended to permanently install devices related to low-voltage wiring in a manner suitable for decontamination. The team also recommends to remove the unused taps. The inspection team noted that the low-voltage exposed wiring in the HCL was placed in suitable electrical boxes. The removal of the unused taps on the down draft tables was not completed, as there was a need for an option to reinstate them. The inspection team suggests consideration be given to the boxing in of the taps to reduce the likelihood of snagging suits on tap protrusions.

**13. Equipment and maintenance**

36. CDC described equipment and maintenance systems during the site visit including the effluent decontamination system, autoclaves, liquid nitrogen stores, fumigation and the plant room. The inspection team examined relevant SOPs and completed validation checklists.

37. The previous report recommended that a documented history of HEPA filter test result values should not only be recorded, but also documented and signed off by authorised CDC staff and that the test results should include values in addition to pass/fail results. The inspection team noted that signatures had been added to the report and test result values for HEPA were included. It was noted that pressure differential tests had been completed annually. HEPA filters were not patched, rather completely replaced.

38. The previous report recommended to review and update *the “Building 18 Maximum Containment Laboratories Wastewater Thermal Decontamination System (Cook*
tanks) Validation Procedure” to reflect information in the service reports. Validation procedure was reviewed by the inspection team.

39. The inspection team did not have any concerns relating to the maintenance of equipment.

14. **Decontamination, disinfection and sterilization**

40. During the visit, the decontamination and inactivation procedures were explained such as gamma irradiation of samples, fumigation of the laboratory space, and autoclaving of equipment and waste.

41. The inspection team reviewed the decommissioning report of the last high containment laboratory shut down. The SOPs and emergency procedures for the thermal decontamination system (cook tanks) were reviewed and found to be adequate.

42. *Observation*: Scenario-based risk assessments for emergency procedures in the event of potentially contaminated effluent spills from the tanks, piping, pumps and valves are beneficial.

15. **Transport procedures**

43. The inspection team were informed that the liquid nitrogen (LN₂) tank in the vault is to be replaced by a new tank to reduce the likelihood of failure as the current tank is old. The current LN₂ tank housed in the vault will be transported to the BSL4 laboratory from which stocks will be transferred to a new one. The newly stocked tank will be transported back to the vault.

44. *Observation*: The procedure and risk assessment document was reviewed by the inspection team. While the procedure was considered to be suitable, it would be useful to have more detailed information about the individual steps of each process involved.

16. **Security**

45. Previous finding (paragraph 51): “There is a rigid security system in place to access the vault and the repository in the laboratory. However, the inspection team has concerns regarding the procedure for the transfer of live variola virus to the gamma cell irradiation. The inspection team recommends a review of that procedure.”

46. Reinforced security for CDC procedures for the transfer of variola virus to the gamma cell irradiator were provided to the inspection team. Finding closed.

47. The inspection team did not have any concerns relating to security.
OVERALL CONCLUSIONS

The WHO inspection team found that CDC had addressed many of the findings raised from the previous 2019 inspection. The continual efforts and commitment of CDC management and staff in ensuring safe and secure processes of work is commendable. The team have made some recommendations from this most recent inspection, which CDC should address accordingly to enhance further the safety and security of the facility.

The intention of the observations and findings described within this report are to recognize best practices and strengthen further the current measures implemented for the safe and secure management of work on variola virus.

In conclusion, there were no major findings observed, however the inspection team recommended some improvements. This inspection report places no responsibility on the WHO. Continued safe and secure conduct of work on live variola virus remains the responsibility of CDC. As such, the WHO requests that CDC propose an action plan to address the issues raised for further improvement. The WHO should receive this action plan within 30 days of receipt of this report.

ACKNOWLEDGEMENTS

The WHO inspection team is grateful for the cooperative discussions held with CDC staff as well as their commitment and hospitality throughout the inspection.