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
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 furnishings 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:

1) the amount and location of equipment in the current laboratory biological safety cabinet; 2) the waste treatment and transportation process at the isolation hospital; 3) the flow of healthcare staff from corridor, to changing room, to patient suites with clear segregation between clean and dirty areas.”

1) Two biological safety cabinets were installed in the new clinical laboratory, though the equipment in the biological safety cabinets needs further consideration and coordination with the workflow.

2) The autoclave for waste treatment in a separate room was inspected by the team. A validation procedure should be added.

3) An SOP was developed for the entry to the patient room determining the PPE being worn and pads on the floor soaked with disinfectant to avoid the spread of infectious agents.
Even though there are some commendable modifications such as the new clinical laboratory, the inspection team sees room for improvement concerning biosafety. Therefore, this previous finding remains open.

31. **Priority 1 Finding:** The inspection team was shown the autoclave and the engineering controls for the air system in the rooms and on the roof. The team recommends a thorough assessment of them and their validation, specifically when dealing with one or more patients with smallpox, for the following:

1) Autoclave, procedure and protection of personnel,

2) HEPA filter, the necessity of a second HEPA filter for maintenance work and/or malfunction,

3) Roof exhaust, address location so as to minimize chance of re-entrainment,

4) Air inlets and outlets of the isolation rooms and the laboratory,

5) Procedures related to handling potentially infectious patients,

6) Effluent treatment.

32. Previous finding (paragraph 37): “A review of the chemical and dispenser style of the hand sanitizer within the patient rooms of the isolation hospital was recommended.” New dispensers were installed and tested by the inspection team. A risk assessment was conducted and revealed that the chemical disinfectant can be used further. The inspection team considers this finding as closed.

**10. Emergency response and contingency planning**

33. Emergency evacuation from the facility was described during a visit to the maximum containment laboratory facility. CDC personnel presented their emergency response plans and exercise drills involving local emergency response units. The inspection team reviewed emergency plans and procedures provided by CDC personnel.

34. Emergency scenarios trained in 2018 included bringing out an unconscious worker by the other workers in the lab.

35. **Observation:** The inspection team recommends including a scenario of an unconscious worker alone in the laboratory in the next emergency training.

**11. Accident and incident investigation**

36. Since the last inspection no incident or accident was reported. The incident reporting system is coordinated centrally by the security operating centre with a standardized notification flow chart helping laboratory staff guiding through the procedure. Incidents and near misses are reported via software, with an option to report anonymously, and then
analysed by the senior leadership. Additionally, the lessons learnt from individual events are shared with the team.

37. The inspection team did not have any concerns relating to accident and incident investigation.

12. Facility physical requirements

38. During the facility visit the inspection team highlighted concerns regarding exposed low-voltage wiring in several places (ceilings/walls) and unused taps on the necropsy table.

39. Observation: The inspection team recommends that devices related to low-voltage wiring be permanently installed in a manner suitable for decontamination. The team also recommends removal of the unused taps.

13. Equipment and maintenance

40. CDC described equipment and maintenance systems during the site visit including the effluent decontamination system, autoclaves, liquid nitrogen stores, fumigation and the plant room. CDC explained how the annual maintenance is initiated and the inspection team examined relevant SOPs and completed validation checklists.

41. Previous ongoing finding (paragraph 49): “Filters (e.g. HEPA) installed as secondary barriers to protect certain pieces of equipment and areas in the containment facility (e.g. door seals, pressure monitoring tubes) in the event of a primary containment failure should be included in the regular maintenance programme”. The inspection team was shown the alternative filters in use. This finding is now closed.

42. Observation: HEPA filters are critical elements in a high containment facility. Therefore, a documented history of test result values should not only be recorded, but also documented and signed off by authorised CDC staff. For best practice, the inspection team recommends values of the test results be added alongside the pass/fail results.

43. Observation: It is also recommended for “Building 18 Maximum Containment Laboratories Wastewater Thermal Decontamination System (Cook tanks) Validation Procedure” be reviewed and updated to reflect information in the service reports.

14. Decontamination, disinfection and sterilization

44. During the visit, the decontamination and inactivation procedures were explained such as gamma irradiation of samples, fumigation of the laboratory space, decontamination of mice with formaldehyde, autoclaving of equipment and waste and chemical disinfection using the dunk tank.
45. The procedure for the fumigation of the maximum containment laboratory facility including the placement of the biological indicators based on the initial validation was explained in detail to the inspectors. The inspection team reviewed the most recent fumigation record along with the fumigation reports of the HEPA filters.

46. Previous finding (paragraph 51): “As variola virus is environmentally stable compared with other Risk Group 4 agents such as Ebola virus, the inspection team recommend a review of

1) the documentation (SOP, recording etc.) for the validation system for the effluent decontamination system, autoclaves and room fumigation as well as virus inactivation procedure;

2) decontamination procedures to include addressing equipment drain lines.”

The inspection team was shown the in 2018 revised SOP for the high containment laboratory waste water treatment decontamination system validation procedure and the validation report of the cook tank. The inspection team recommends adding the results of the biological indicator to the cook tank validation report for best practice. The drain lines of the necropsy table are not used with the current procedure, but are under review and with this the finding is now closed.

47. The inspection team did not have any concerns relating to decontamination, disinfection and sterilization.

15. Transport procedures

48. CDC has detailed instructions describing the packaging and transportation of live variola virus and variola DNA for the purpose of gamma irradiation performed within the same building complex to inactivate the virus. The inspection team examined logbooks for the transfer of live variola virus to the gamma irradiator.

49. The inspection team did not have any concerns relating to transport procedures.

16. Security

50. Security precautions were observed during the visit of the Maximum containment laboratory, the vault, closed circuit television (CCTV) room (Security Operation Centre) and the contracted isolation Hospital. Additionally, CDC presented the applied security measures of the campus, information and personnel.

51. Priority 1 Finding: 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 for the purpose of inactivation from the designated maximum containment laboratory to the gamma cell irradiation room located in the same building complex. The inspection team recommends a review of that procedure.
**OVERALL CONCLUSIONS**

52. The WHO inspection team found that CDC had addressed many of the findings raised from the previous 2017 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.

53. 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.

54. 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.