WHO/WHE/CPI/2018.15

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, 8-12 May 2017

April/2018

World Health Organization

Suggested citation. 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, 8-12 May 2017. Geneva, Switzerland: World Health Organization; 2017. Licence: CC BY-NC-SA 3.0 IGO.

Cataloguing-in-Publication (CIP) data. CIP data are available at http://apps.who.int/iris.

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Report from the World Health Organization Biosafety Inspection of the Variola Virus Maximum Containment Laboratories to the Centers for Disease Control and Prevention

Atlanta, Georgia, United States of America, 8-12 May 2017

EXECUTIVE SUMMARY

The WHO team of international experts carried out a biosafety inspection at one of the two WHO-authorized variola virus (causative agent of smallpox) repositories: CDC*, in May 2017 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 high-containment facilities, the supporting engineering systems and the long-term secure specimen storage arrangement and the isolation hospital. Before entry into the high-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), logbooks, meeting minutes, floor plans and other 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 2015, 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 2017 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 from CDC 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 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 annual maintenance of the facilities, following decontamination. 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 8th to the 12th of May 2017 to meet the biennial inspection requirement of resolution WHA60.1. On the 7th 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 2010, 2013 and 2015 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 security.
- 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 high-containment facility designated for research with variola virus, its supporting mechanical systems, the long-term specimen storage repository and the isolation hospital. Two inspection team members were permitted to enter the restricted-access, long-term variola virus specimen storage area.

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, floor plans 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 and provided documentation of the policies, processes and procedures supporting their biological risk management system within their facility. The inspection team overviewed the document hierarchy in terms of national and international regulations, and 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, institutional audits and other relevant documents.

11. CDC has implemented significant improvements in the internal management accountability for biosecurity, including staffing new positions since the last inspection. The biological risk management system and approval processes of CDC incorporates several levels of management, the national regulatory authority and dedicated biosafety committee members. These were demonstrated through presentations and by the provision of documentation including federal inspection audits for biosafety compliance and training records.

12. CDC also presented various new institutional committees and boards, many of which have been established since the last WHO inspection including the biosecurity board, biosafety committee, laboratory safety review board, laboratory safety training board and laboratory quality council. The inspection team examined the latest CDC's high-containment laboratories (HCL) governance council report, which corroborated the implementation of the various committees and boards.

13. The previous inspection report[1] noted the following ongoing finding (paragraph 18): *"(improved biological risk management system): CDC is making substantial progress in setting up a comprehensive system for managing biological risk associated with* variola virus *research. The fourth previous finding (17) on adoption of a formal management system is still open"*. The inspection team observed evidence for adoption of a formal management system including transitioning to an electronic format for document control and approval. This finding is now closed.

[1] 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, 9-20 May 2015

2. Risk assessment

14. CDC representatives presented a structured governance process for risk assessment and the inspection team reviewed a number of risk assessments and SOPs. CDC also demonstrated the implementation of a new electronic system for record keeping.

15. The previous inspection report noted the following finding (Paragraph 21): *"…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, and now controlled through a structured governance process. There is evidence that CDC is making positive steps to implement a maintenance programme. However, as this is still in development the finding remains open.

16. The previous inspection report noted that one finding (22 from the 2013 inspection), on a comprehensive, systematic approach, is still open: *"Work should continue to further develop policies, methodologies and tools to ensure a comprehensive and systematic approach to risk assessment is set in place for all work with* variola virus*"*. The inspection team observed that CDC has made significant improvements to the risk assessment process. This finding is now closed.

3. Pathogen and toxin inventory and information

17. The inspection team examined the working stock and long-term storage areas for variola virus and viral DNA as well as the instruction manual and logbooks of these materials. The process for recording and inventorying working and archival collections is well controlled which includes a new restricted access electronic database system with an automated audit trail. In addition, verification by the U.S. Federal regulators occurs on an annual basis.

18. The material transfer process to remove materials from the variola virus containment laboratory including packaging of samples was demonstrated by CDC (see Section 6) and logbooks examined by the inspection team.

19. *Observation:* The detailed electronic inventory system implemented represents a best practice.

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. CDC staff presented the inspection team with information on occupational health and safety and demonstrated an electronic system for documents and training, which will include an automated approval process via email from authorized persons and incorporate predefined responsibility levels for various document types. This system is still in the development stages and scheduled to go live before the next WHO inspection.

22. Various training courses required to be completed by laboratory personnel were highlighted to the inspection team along with a laboratory science safety symposium that was held in 2017.

23. *Priority 2 finding:* Previous finding (paragraph 30): *"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"*. Signatures and dates for training records are in place for the trainees, however there needs to be consistent additional sign off by the trainer. Therefore, this finding remains open.

6. Good microbiological practices

24. The variola virus stocks are stored in the vapour phase of the liquid nitrogen for safer sample storage .

25. *Observation:* The inspection team reviewed various SOPs throughout the visit. CDC demonstrated the material transfer to the irradiation suite, which included the process for packaging of samples. This process was considered best practice by the inspection team.

26. Previous finding (paragraph 33): *"The inspection team recommends that the CDC use a method to record microbiological practices (e.g. archived CCTV material) for future inspections, so that the team can verify that they are conducted in accordance with written procedures"*. Captured CCTV material is held for a set period that can allow for any security breach investigation. The inspection team selected to observe archival video footage of a material transfer event that aligned with safety, security and written procedures. A training regime including refresher training for procedures along with SOPs were provided to the inspection team, which included a two-person rule for critical steps. The inspection team consider this satisfactory to close this finding.

7. Clothing and personal protective equipment

27. The inspection team examined some of the personal protective equipment (PPE) in the Biosafety Level 4 (BSL-4) facility. The inspection team recommended a review of the taping procedure for the glove-suit junction.

28. The inspection team reviewed SOPs including one for suit tear repair. CDC personnel highlighted that the suit material was cleaned prior to the addition of tape, which had not been made clear in the current SOP. CDC stipulated that the SOP would be up-dated to clarify this point.

29. Previous finding (paragraph 36): *"The inspection team noted that the current coupling device that connects a supportive air hose to the positive pressure suit for biological containment has*

repeatedly trapped gloves, and an alternative design should be considered". New coupling devices and air hoses are in the process of being purchased and fitted, and an in-place example was shown to the inspection team. The design of the new coupling device was shown to greatly reduce the risk of trapping gloves. In the interim new gloves had been purchased to reduce the risk of them being trapped in the current coupling devices. This finding is now closed.

8. Human factors

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

9. Healthcare

31. The vaccination policy to visit the long-term storage vault had been changed and implemented following a revised risk assessment. The risk assessment that had been approved by one of the safety boards was examined by the inspection team.

32. The inspection team also discussed this element with the medical staff during a visit to the isolation hospital for highly dangerous infections. This hospital makes it possible to accommodate CDC personnel conducting work with variola virus, for quarantine and/or treatment. Discussions included how potentially exposed staff would enter the facility, caring for staff, the types of equipment including PPE used, and general operation and maintenance of the facility.

33. Medical staff explained that the isolation hospital is currently under renovation, which is scheduled for completion prior to the next inspection.

34. The vaccination programme policy for accessing the vault was up-dated based on a risk assessment highlighting that vaccination was not necessary. This brought it in line with the vaccination policy for the laboratory during down time.

35. Previous finding (paragraph 42): *"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) This isolation hospital is currently looking into, but has yet to purchase, alternative soft furnishings better suited to decontamination. In addition, the fumigation validation protocol for the patient rooms and laboratory (including ceiling voids) was requested, but not received, by the inspection team therefore this part of the finding remains open. 2) A new laboratory facility is under construction that includes an ante-room and new doors to allow for effective decontamination. However, as the laboratory is still under construction, this part of the finding remains open. 3) Pressure monitoring devices were in place to gauge negative pressure gradation between ante-room and patient rooms and monitored continuously. Therefore, this part of the finding is now closed.

36. *Priority 1 finding:* 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.

37. *Priority 1 finding:* A review of the chemical and dispenser style of the hand sanitizer within the patient rooms of the isolation hospital was recommended.

38. Observation: Medical staff highlighted that refresher training for the donning and doffing of PPE within the isolation hospital is carried out every three months. This was considered a best practice by the inspection team.

10. Emergency response and contingency planning

39. Emergency evacuation from the facility was described during a visit to the laboratory facility. CDC personnel presented their emergency response plans and exercise drills involving local emergency response units. Lessons learnt and recommendations for implementation were also highlighted. The inspection team reviewed emergency plans and procedures provided by CDC personnel.

40. Previous finding (paragraph 45): *"It is recommended that CDC continue to coordinate the interaction of external emergency responders with their internal technical personnel in order to ensure that containment is not breached as a result of emergency interventions"*. Emergency response training exercises have been undertaken and included coordination with external local emergency responders and internal personnel. Lessons learned from these exercises have been documented and are in the process of being followed up. This finding is now closed.

41. Previous finding (paragraph 46): *"It is well recognized that the air systems in many types of suits used in BSL-4 laboratories result in a high noise level. We recommend that CDC explore whether modern in-suit radio systems could be used for communication during both normal operations and in emergencies"*. Earplugs are worn at all times during wearing of the air-fed suits. Whilst researchers seem content with this method, appropriate communication systems are being investigated. To date, an appropriate communication system meeting biosecurity requirements (e.g. with appropriate encryption) has not been found. This finding is now closed.

11. Accident and incident investigation

42. CDC staff presented policies and procedures relating to accident and incident investigation. The inspection team examined incident and near miss reports since the last inspection along with check lists for risk mitigation and the incident response plan. CDC highlighted the launch of a safety reporting awareness communication campaign to encourage the reporting of near misses.

43. Previous finding (paragraph 48): *"The inspection team recommends that a method that includes structured root cause analysis be used in all incident investigations"*. Root cause analysis was shown to be included in the new standardised incident investigation form. This finding is now closed.

12. Facility physical requirements

44. The inspection team reviewed the fumigation validation record along with logbooks and SOPs for entry into the laboratory facility. Checklists of daily safety inspections for elements of key importance were examined by the inspection team.

45. Previous finding (paragraph 53): "*The team identified particularly critical biocontainment barrier elements (e.g. HEPA filters on showers, process vent filters on cook tanks and filters on soil vent pipes) that are subject to environmental stress (e.g. high humidity and high temperatures). When the facility is re-commissioned, the operational limitations of these installations should be reviewed to establish and document critical limits for pressure, humidity and temperature that could compromise their performance. This information is essential so that operational staff can monitor, maintain and potentially re-test the containment infrastructure*". The over pressurization relief vents of the effluent decontamination system and the plumbing vent system have filters with new isolation valve and decontamination ports. This finding is now closed.

46. *Observation:* CDC has incorporated the improvements of the variola virus containment facility to the other BSL-4 and BSL-3 suites demonstrating a commitment to an overarching systemic improvement approach.

13. Equipment and maintenance

47. 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.

48. Previous finding (paragraph 56): *"A risk assessment should be conducted to examine the design of the vacuum filtration systems on both autoclaves to validate their suitability in BSL-4 laboratories. The standard operating procedure (SOP) for the autoclaves should be modified to include regular tests for leaks"*. CDC provided the inspection team with information to show modification to the autoclave cycle had been undertaken. This finding is now closed.

49. *Priority 2 finding:* Previous finding (paragraph 57): "*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 learned that alternative filters are currently being researched. This finding remains open.

14. Decontamination, disinfection and sterilization

50. CDC staff delivered information related to the workings of the autoclaves, animal waste treatment, pass-through box disinfection and fumigation, and sewage waste treatment to the inspection team. The inspection team examined decontamination protocols, records of inactivation procedures, and validation data from autoclaved waste, waste sewage treatment and fumigation using biological indicators. Before entry into the high-containment facility, the inspection team performed a detailed review of the recent decontamination process. The process of irradiation of samples was also described in detail during a tour of the facility.

51. *Priority 2 finding:* 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 validation documentation (SOP, results etc.) for virus inactivation, effluent decontamination, autoclaves and room fumigations; 2) decontamination procedures to include addressing equipment drain lines.

15. Transport procedures

52. CDC described the transportation of material in detail. The inspection team examined logbooks of transfer and irradiated samples.

53. *Observation:* The inspection team were shown the packaging process and system used to transport samples out of the variola virus containment laboratory. The inspection team selected and observed a piece of CCTV footage of a documented transfer. This procedure was identified as a best practice.

16. Security

54. CDC described an extensive system for ensuring the physical security, security of material, information security and personnel security. The inspection team had the opportunity to verify various security access layers during the site visit. There is an effective system for securing the archival stocks as well as for protecting sensitive information and data. There are well-documented internal duties and instructions for external authorities as well as procedures for IT personnel and visiting scientists and guests.

55. The inspection team did not have any concerns relating to security.

OVERALL CONCLUSIONS

56. The WHO inspection team found that CDC had addressed many of the findings raised from the previous 2015 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.

57. In order to ensure continuity between inspections and to strengthen the inspection and reporting process, the use of a self-assessment form for biological risk management will continue. Each repository is requested to update the sections where changes have taken place since the last inspection and submit it in advance to the next visit.

58. The intention of the observations and recommendations 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.

59. 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.