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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, 8-12 May 2017

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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.