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

Atlanta, Georgia, United States of America, 9–20 May 2015

EXECUTIVE SUMMARY

The inspection was carried out at one of the two WHO-authorized variola virus (smallpox) repositories, the Centers for Disease Control and Prevention (CDC) in the United States of America, in May 2015 by the WHO team of international experts, in accordance with World Health Assembly resolution WHA60.1 (2007), as agreed by all relevant parties in a preparatory meeting before the visit.

The activities of the WHO team included inspection of the physical high-containment facilities designated for research use of variola virus, the supporting engineering systems and the long-term secure specimen storage arrangement. The team also heard presentations from and had interactive discussions with CDC staff and reviewed records, regulatory instruments, instruction manuals, meeting minutes, floor plans and other documents that they requested.

The CDC management and staff described in detail their institutional commitment to biosafety and biosecurity and their facility systems and operations throughout the inspection. The observations and findings were presented and discussed with CDC on the last day of the inspection. CDC has also completed a new self-assessment form to identify updates and modifications since the previous inspection, to provide continuity between inspections.

Improvements have been made since the previous inspection, in 2012, with many findings addressed and closed. During the 2015 WHO inspection, no finding that required immediate corrective action (Priority 3) was identified, although further work was requested on some issues.

In conclusion, the CDC repository was found to meet international levels of biosafety and biosecurity for variola virus research and storage. CDC remains, however, responsible for the continued safe, secure storage of and conduct of work with live variola virus; this inspection report places no responsibility on WHO. CDC is requested to present to WHO an action plan to address the issues raised for further improvement within 30 days of receipt of this report.

CONTEXT

1. World Health Assembly resolution WHA60.1 (2007) requests WHO to inspect the two authorized repositories of variola virus every two years, namely, the State Research Centre of Virology and Biotechnology (VECTOR) in the Russian Federation and the Centers for Disease Control and Prevention (CDC) in the United States of America. This mandate is intended to ensure that the conditions of storage of the virus that causes smallpox and of research conducted in the laboratories meet the highest requirements for biosafety and biosecurity. In addition, resolution WHA60.1 requests that inspection-mission reports be made available for public information after appropriate scientific and security redaction.

2. The WHO inspection team, consisting of international experts in a range of fields, visited CDC and its contracted facilities from 9 to 16 May 2015 to meet the biennial inspection requirement of resolution WHA60.1. The visit was extended to 21 May in order to accommodate the staggered arrivals of observers from VECTOR. Colleagues from CDC and part of the WHO team met with the VECTOR colleagues for 3 days to exchange information on recent changes, improvements and best practice in an open, collegial spirit. The previous inspection took place in May 2012. To ensure an equitable process, it was agreed to alternate the order of facility inspections for this biennial term.

3. In view of the inherent technical complexity and sensitivity of the issue, WHO organized a preparatory meeting in advance of the on-site inspection at its headquarters in Geneva, Switzerland, on 22–23 October 2014, between representatives of the two repositories and the designated inspectors. The participants reviewed the inspection practices and protocol to be followed and confirmed the inspection framework, which included the dates of the visits, the draft agenda and the inspection protocol. The dates for inspection of both repositories were planned to coincide with the annual maintenance of the facilities, when they are decontaminated. While this allows the inspectors to enter areas of the facilities that are difficult to access when live variola virus is being handled, it obviates observation of actual procedures and operations. For future site visits, viewing of archived videos that capture actual work will be explored as a complementary means for realistic observations.

4. The preparatory meeting also achieved consensus that representatives of the other repository could participate in the inspection as observers. They are permitted to attend the inspection, except in closed discussions among the WHO inspection team and during the session in which the findings and recommendations of the team are presented to the repository in question, in order to ensure parity and the impartiality of the inspection, as clarified by the WHO Office of the Legal Counsel.

INSPECTION PROGRAMME

5. By agreement with both repositories, the present inspection included the elements defined in the protocol used in the 2009 and 2012 inspections. The protocol is based on the European Committee for Standardization (CEN) Workshop Agreement (CWA) 15793 (2008) document. The CWA document is used to structure the inspection, including a method to follow up previous “findings” and “observations”.

6. The CWA 15793 was not used or intended to be used to assess the facility for conformity. In this regard, the inspection team and repository representatives agreed to use a transparent rating scale to categorize findings at the two repositories.

7. The findings were rated on a four-level scale to ensure clarity and a consistent approach at the two repositories. The following categories were used:

- Observations are positive remarks, including examples of robust controls or other best practices, and 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.

8. CDC completed a CWA 15793 clause-by-clause self-assessment form (provided by WHO before the inspection), which contributed to the audit evidence.

9. The on-site inspection was conducted over eight working days, three days having been added owing to the lengthy arrangement for inclusion of observers from VECTOR. The eight days also included internal discussions in the WHO team and presentation of the findings and recommendations to CDC staff on the last day. The wrap-up session provided an opportunity to discuss and confirm the WHO inspection team's understanding, observations and recommendations.

10. The WHO inspection team heard presentations from and held interactive discussions with CDC staff, made a detailed review of records, regulatory instruments, institutional rules, instruction manuals, meeting minutes, floor plans, air and waste flow diagrams that the WHO inspection team had specifically requested in advance. The visit included on-site inspection of the physical high-containment facility designated for research with variola virus, its supporting mechanical systems and the long-term storage repository. CDC staff explained their facility systems in detail throughout the inspection.

11. To meet internal CDC requirements, only WHO inspection team members who had proof of recent vaccinia vaccination were permitted to enter the restricted-access long-term variola virus specimen storage area.

12. In conclusion, no finding requiring immediate corrective action (Priority 3) was identified, although some issues were considered to require improvement. CDC is requested to propose to WHO an action plan to address the issues raised for further improvement within 30 days of receipt of this report.

13. The findings of the WHO inspection team are presented below. Their aim is to reduce risk and encourage further use of best practices. While every effort was made to assess the facility, documents and current practices, it should be noted that the inspection was carried out over a limited time, when the facility was decontaminated, so that no actual work was observed.

14. The WHO inspection team appreciated the collaborative attitude and committed engagement of the CDC management and all responsible staff throughout the inspection.

1. Biological risk management system

15. CDC described new processes established since the previous inspection, such as a new high-level governance structure and new risk assessment and laboratory safety training (in place or being established), such as the creation and filling of a new senior biosafety leadership position, for which the roles and responsibilities are still being defined. The biological risk management programme also includes new steps for the enhancing the culture of biosafety, improved incident reporting and sharing of best practices.

16. The discussions, presentations and documentation provided by CDC to the onsite inspection team and the response to the previous inspection report indicate that CDC senior management has

supported incorporation of many new elements to improve CDC's general biological risk management programme.

17. The previous inspection report[1] noted four findings. The information provided resulted in closure of three findings (18, 19, 20) relating to the CDC biosafety manual, the biorisk target and tracking of actions, respectively.

18. *Priority 2 finding (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.

2. Risk assessment

19. The CDC has identified "risk assessment" as a primary tool for managing all aspects of biological safety within the organization. At institutional level, training in risk assessment is being provided to all scientific staff; system-wide processes for documentation are being developed and will be used in 2015.

20. *Observation*: The enhanced risk assessment process is being used to determine the appropriate biological safety level (BSL) for prospective work. The variola programme includes use of best practice in risk assessments of procedures. For example, this approach has been used to examine virus inactivation and other laboratory procedures. The samples used in these risk assessments provided reassurance that the necessary detail and information are present. This process is commendable.

21. *Priority 2 finding*: The inspection team was informed that 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. A systematic approach can result in continuous improvement, with input from specialists who manage the same or similar processes in closely related disciplines; 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 change control should be reviewed, with documented input from all internal stakeholders.

22. The previous inspection report noted that one finding (22), on a comprehensive, systematic approach, is still open.

3. Pathogen and toxin inventory and information

23. The inspection team was given an overview of the poxvirus inventory programme, including the system used for record-keeping. The overview included a review of the restricted-access systems and other biosecurity elements (e.g. rooms and freezers). The role of the national regulatory authority in reviewing this system annually was discussed.

[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, USA, 7-11 May 2012. Geneva: World Health Organization; 2013.

24. The inspection team concluded that the CDC has a well-established process for recording and inventorying its working and archival collections. No concerns were noted.

4. General safety

25. Procedures are in place for meeting the requirements for general safety in the facility. Observations on general safety are made only as part of those on other biosafety and biosecurity elements.

26. Since the previous inspection, the CDC has made some improvements, including addition of an automatic dispensing system for the large volumes of chemical required for the chemical shower. This process was significantly improved by reducing manual handling and the risks for exposure. The CDC provides hearing protection at access points to noisier plant rooms. The previous recommendation (26) is thus addressed.

27. The previous inspection raised an issue about the two-person rule for especially critical material or operations in place at CDC. Discussions with the inspection team indicated that the principle concerns are: 1) the duty of care regarding general health and safety and 2) ensuring that laboratory biosecurity reduces the risk of unauthorized removal of "select agents". CDC conducted internal reviews and concluded that a number of alternative mechanisms are in place to minimize these risks. The inspection team was satisfied with the arrangements, and previous finding (25) is now closed.

5. Personnel and competence

28. CDC provided an extensive description of their mandated training activities, including institutional requirements such as relevant record-keeping. The training programme is clearly extensive, rigorous and focused on safety.

29. *Observation*: The CDC variola programme has a consolidated system for records of training for all relevant programme staff, which represents good practice. The inspection team recommends that the same process be used to consolidate other records, such as those described in the procedure manual for building 18. The inspection team concluded that CDC has a well-established process for managing personnel and their competence. The previous finding (28) is now closed.

30. *Priority 1 finding*: 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.

6. Good microbiological practices

31. CDC provided details of the inclusion of safe handling of highly pathogenic microorganisms in the training and standard documentation of microbiological and special practices applicable to all BSL-4 facilities at CDC. The smallpox-specific experimental protocols and the daily checks done on entry into the BSL-4 area reflect a commitment to good microbiological technique. Personnel handling animals undergo regular re-training. CDC has a team of veterinarians and animal technicians, and the containment areas are served by a selected group of technical staff with special training. The inspection team had no opportunity to observe adherence to good microbiological technique during active work with variola virus, as the inspection was made during the annual shut-down of the facility. Practices and procedures in animal handling were discussed in order to minimize the potential release of infectious aerosols into the animal room or the main laboratory.

32. The previous inspection noted that primary containment should be reviewed with regard to animal holding and procedure rooms during work with non-human primates. This review has been completed, and the previous finding (30) is closed.

33. *Priority 1 finding*: 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.

7. Clothing and personal protective equipment

34. CDC presented and provided documentation of new procedures for the selection, use, maintenance, repair and decommissioning of suits and gloves. The inspection team was informed that studies had been performed to establish the maximum usage of gloves (time or frequency, whichever is less). As a result, CDC has standardized the gloves to be used routinely and excluded models with unsatisfactory performance. The previous inspection had some concern about the gloves being used and possible issues with the integrity of the personal protective equipment (i.e. the positive pressure suit) being used. In view of the above information, the finding (31) is now closed.

35. *Observation*: CDC's in-house glove testing protocol is an excellent best practice for evidence-based decision-making.

36. Priority 1 finding: 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.

8. Human factors

37. Management of risks due to human factors for people who work in or maintain the facility was discussed. Details were provided of regular training, personal suitability assessments (upon hiring and annually thereafter), enhanced security clearance and medical monitoring, all of which are required for people who have access to the facility.

38. No findings were reported after the previous inspection. The CDC research team continues to show good collegiality and cooperation, with regular meetings to ensure communication. The inspection team had no concern about the practices presented.

9. Health care

39. The CDC variola occupational health programme is based on Federal regulations for activities involving the select agents and toxins. These include pre-placement examinations, medical surveillance, access to clinical occupational health services, immunization programmes, respiratory protection programmes, emergency medical evaluation and post-exposure management as well as isolation protocols for the neighbouring emergency care facility.

40. The CDC variola programme includes a well-established vaccination and annual medical examination programme. Employees working with variola virus are vaccinated every three years. The policy also applies to visitors, animal caretakers, maintenance personnel, first responders and certain health care personnel who have access to the laboratories when variola virus is present.

41. The previous inspection report noted that the level of preparedness and the appropriateness of the contracted hospital isolation unit for handling variola-infected patients should be reviewed. The inspection team had the opportunity to visit the hospital isolation unit, where patient handling and procedures were explained. Recent use of this facility to treat patients with Ebola virus disease resulted in a number of improvements to the facility and equipment and updating and in-use testing of operational protocols, which are also applicable to variola. A core team of vaccinated staff is regularly trained in the procedures, including handling patients and use of personal protective equipment. Given these observations, the previous inspection report finding (35) is now closed.

42. *Priority 2 finding*: 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.

10. Emergency response and contingency planning

43. The inspection team was given an overview of the emergency management system and the dedicated team for emergency preparedness. The CDC site is well prepared to manage possible emergencies, with particular attention to local weather events (e.g. tornadoes) and the possibility of long-term power failures. The CDC campus is served by multiple redundant power systems, and the reliability of the back-up electric power systems is tested annually. The previous inspection report noted some concern about how emergency situations would be detected. CDC provided an outline of how such events would be detected and contained. This finding (37) is therefore closed.

44. *Observation*: CDC has in place a well-established process of emergency planning and accident rehearsals, which was outlined in the documents and in presentations to the inspection team.

45. *Priority 1 finding*: 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.

46. *Priority 1 finding*: 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.

11. Accident and incident investigation

47. CDC recently revised the general emergency management structure and adapted its integrated management plan for emergencies. Regular drills and tests are conducted, including medical emergencies in the laboratory. CDC has a clear reporting system for incidents and accidents, which is based on Federal regulations and institutional documents. The variola programme maintains records of all incidents and their resolution.

48. *Priority 1 finding*: The inspection team recommends that a method that includes structured root cause analysis be used in all incident investigations.

49. No accidents were reported during the period since the previous WHO inspection. One incident related to a pinched glove was documented, with details of follow-up actions; appropriate measures were taken.

50. *Observation*: The CDC variola programme is to be commended for its efforts to establish and maintain a comprehensive incident logging system.

12. Facility physical requirements

51. The WHO team noted the dedication and competence of the engineering and technical support staff. The level of specialization at CDC is possible in only a few large-scale facilities. The research team works in a modern facility that is well designed to support their research. The facility has been in operation for approximately 10 years, and critical biocontainment systems (e.g. effluent pipework integrity) should shortly be re-commissioned to ensure that any risk paths associated with a single protection layer are fit for purpose and are maintained if a condition-based maintenance regime is introduced.

52. Clearly defined procedures are in place for shutting down, decontaminating and reassigning the animal room as a space that could be attached to either the BSL-4 or the BSL-3 laboratory.

53. *Priority 2 finding*: 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.

54. CDC provided documentation and held discussions with the inspection team to close the previous finding (41), indicating that the systems in place meet the intent of *Biosafety in Microbiological and Biomedical Laboratories*, 5th edition.

13. Equipment and maintenance

55. The facility relies on a vast variety of equipment to support the laboratories. Different groups are responsible for maintaining or overseeing maintenance by external companies and are coordinated by the high-containment laboratory oversight group. The records reviewed included those for biosafety cabinets, which indicate that biocontainment equipment is tested regularly.

56. *Priority 2 finding*: 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.

57. *Priority 2 finding*: 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.

58. CDC provided documentation and held discussions with the inspection team to close the previous finding (43), as the relevant SOPs and practices are in place.

14. Decontamination, disinfection and sterilization

59. CDC has established procedures and protocols for decontaminating its facilities and inactivating waste. Documentation was provided to show that the autoclave procedures used to decontaminate

loads are effective. The documentation included validation studies to resolve the outstanding element of the previous report, and the finding (45) is closed.

60. For maintenance, the laboratory suite is treated with vaporized hydrogen peroxide. A number of improvements have been made to preparation of the laboratories since the previous inspection to address finding (44). Although a formal risk assessment of the process was not presented, improvements were noted.

61. *Observation*: Vaporized hydrogen peroxide decontamination is done by trained staff who are experienced in the process. It is commendable that dedicated staff specialized in this process are used, to ensure the highest standards of application.

15. Transport procedures

62. CDC has a rigorous system of internal transfer and approvals. All transfers must be announced, documented and witnessed. Materials are removed according to standard operating procedures and must not leave the custody of a variola programme staff member at any time.

63. CDC confirmed that there was no transfer of material to the vault and no external shipment of DNA or live variola virus during the reporting phase. In 2014, material for diagnostic purposes was transferred for inactivation on three occasions; the "chain of custody" of all material was maintained. The inspection team concluded that CDC has a well-established system for secure, safe transport of materials. No concerns were noted.

16. Security

64. CDC described an extensive system for ensuring the physical security of the laboratories, the surrounding spaces and the people who work on site. CDC is subject to regulatory requirements for selected agents, including recent introduction of "top secret" clearance for anyone who has unescorted access to variola virus. Archival and working stocks are kept in highly secure environments, and sensitive data and information are also secured. The inspection team concluded that CDC has a well-established, highly effective system for securing its premises and ensuring the reliability of its staff. No concern was noted.

OVERALL CONCLUSIONS

65. In comparison with the previous inspection, in 2012, the WHO team found that many improvements had been made and that the recommendations of the previous report had been largely addressed. The efforts and organizational commitment of the CDC top management and staff are commended. Some issues were found, however, which should be addressed according to their rated priority in a continuous effort to further enhance the safety and security of the repository.

66. It is expected that a biological risk management self-assessment form will continue to be used and provided by WHO before the next inspection as an important follow-up tool to ensure continuity between inspections and to strengthen the inspection and reporting processes.

67. This inspection report places no responsibility on WHO for the safe, secure conduct of work with live variola viruses, which remains the responsibility of the CDC management and its staff. The observations made above are intended to recognize best practices, and the recommendations are intended to further strengthen the current arrangements for the safe, secure conduct of work on variola viruses.

ACKNOWLEDGEMENTS

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