



**Report of the World Health Organization Biosafety Inspection
Team of the Variola Virus Maximum Containment
Laboratories
to the State Research Centre of Virology and Biotechnology,
Federal Service for Surveillance on Consumer Rights
Protection and Human Well-being**

**Koltsovo, Novosibirsk Region, Russian Federation
8–13 December 2014**

EXECUTIVE SUMMARY

The inspection was carried out at one of the two WHO-authorized variola virus (smallpox) repositories, the State Research Centre of Virology and Biotechnology (“VECTOR”) in the Russian Federation, in December 2014 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 VECTOR staff and reviewed records, regulatory instruments, instruction manuals, meeting minutes, floor plans and other documents that they requested.

The VECTOR 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 VECTOR on the last day of the inspection. VECTOR 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 2014 WHO inspection, no finding that required immediate corrective action (Priority 3) was identified, although further work was requested on some issues.

In conclusion, the VECTOR repository was found to meet international levels of biosafety and biosecurity for variola virus research and storage. VECTOR 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. VECTOR 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 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 VECTOR from 8 to 13 December 2014 to meet the biennial inspection requirement of resolution WHA60.1. The previous inspection took place in October 2012. 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.

3. 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

4. By agreement with both repositories, the present inspection included the elements defined in the protocol used in the 2008 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”.

5. 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 the findings at the two repositories.

6. 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.

7. VECTOR completed a CWA 15793 clause-by-clause self-assessment form (provided by WHO before the inspection), which contributed to the audit evidence.
8. The on-site inspection was conducted over six working days, which included internal discussions in the WHO team and presentation of the findings and recommendations to the VECTOR staff on the final day. The last session provided an opportunity to discuss and confirm the WHO inspection team's understanding, observations and recommendations.
9. The WHO inspection team heard presentations from and held interactive discussions with VECTOR staff, made a detailed review of records, regulatory instruments, institutional rules, instruction manuals, meeting minutes, floor plans and air and waste flow diagrams that the WHO inspection team had specifically requested in advance and additionally requested as necessary. The visit included a one-day on-site inspection of the physical high-containment facility designated for research with variola virus, its supporting mechanical systems and the long-term specimen storage repository. The site was visited a second time to inspect the facility in greater technical detail. VECTOR staff explained their facility systems in detail throughout the inspection.
10. To meet internal VECTOR requirements, only WHO inspection team members who had proof of vaccinia vaccination in the preceding five years were permitted to enter the restricted-access long-term variola virus specimen storage area.
11. In conclusion, no finding requiring immediate corrective action (Priority 3) was identified, although some issues were considered to require improvement. VECTOR 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.
12. 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.
13. The WHO inspection team appreciated the collaborative attitude and committed engagement of the VECTOR management and all responsible staff throughout the inspection.

1. Biological risk management system

14. VECTOR presented and provided supporting documentation of the strategic goal and objectives of the institutional biological risk management policy, which includes compliance with all legal requirements, conducting risk assessments, documentation, communication of roles and responsibilities, continuous improvement and providing information to employees. The main goal of the policy is to detect adverse events and minimize any potential effects.
15. The discussions and the documentation provided demonstrated that senior management and the national regulatory authority are well integrated in the biological risk management system and in the approval processes of VECTOR.
16. VECTOR gave an example of systemic implementation of review and improvement to reduce biological risks.

17. The previous inspection report¹ noted that updates to the instruction manual were needed. As these have been completed, the previous finding (18) is closed.

18. *Observation:* VECTOR has made substantial progress in developing a comprehensive management system for biological risk associated with variola virus research.

2. Risk assessment

19. VECTOR presented their risk assessment process, including the hierarchy for review and senior management approval.

20. During the inspection, the risk assessment for moving micro-isolator animal cages, between rooms within containment was discussed. The inspection team noted that use of micro-isolating caging systems with only a single "layer" of primary containment to hold and move infected animals between rooms poses a risk of "spillage" if a cage is dropped and releases contaminated animals.

21. The previous inspection report noted that the risk assessment method and recording mechanisms should be further developed. While VECTOR has made substantial improvements in this area, this finding (19) is still open.

22. *Observation:* Risk assessment and steps for mitigating the risk associated with specimen movement are in place. Specimens are moved safely and securely within the containment facility: biological samples are sealed in primary vials and only then are transported in robust, hermetically sealed secondary containment.

23. *Priority 2 finding:* While the administrative controls are clearly defined in VECTOR's risk assessment process, estimation of likelihood and consequence could be further developed. Such enhanced assessment would allow formal comparison and prioritization of risks and of the controls of choice. This would better demonstrate how the organization applies the hierarchy of hazard controls. The inspection team considers this a central safety concept and suggests that it be integrated into the VECTOR decision process.

24. *Priority 1 finding:* The risk assessment process flow diagram defines the intended flow of information. The inspection team suggests that a feedback loop from senior management to the research group be added.

3. Pathogen and toxin inventory and information

25. Members of the inspection team had an opportunity to inspect the working stock and long-term storage areas for virus, viral DNA and variola virus genome. This included a review of the restricted access systems and other biosecurity elements (e.g. on rooms and freezers) that are in place.

26. A "chain of custody" has been established to track the fate of materials after they are inactivated and removed from the containment area.

¹ Report of the World Health Organization (WHO) Biosafety Inspection Team of the Variola Virus Maximum Containment Laboratories to the State Research Centre of Virology and Biotechnology ("SRC VB VECTOR"), Federal Service for Surveillance on Consumer Rights Protection and Human Well-being, Novosibirsk Koltsovo, Novosibirsk Oblast, Russian Federation 3-9 October 2012. Geneva: World Health Organization; 2013.

27. VECTOR now has a well-established process for recording and inventorying its working and archived collections. The process has been extended to inactivated materials removed from containment. All materials are logged and catalogued, and designated individuals are responsible for the accuracy of the collections. VECTOR has established stringent rules regarding personal responsibility and accountability. The previous finding (21) is now closed.

28. *Priority 1 finding:* The inspection team recommends that VECTOR's instruction manual clarify the WHO requirements for the transfer of full-length viral DNA more explicitly and state that no site other than the two collaborating centres is allowed to acquire more than 20% of the variola virus genome.

4. General safety

29. 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.

30. The previous inspections noted an issue with the emergency shower. Since the previous inspection, a new emergency shower has been installed, and the item (23) is now closed.

31. *Priority 2 finding:* The current fumigation process has been validated and is verified regularly with biological indicators. The inspection team noted, however, that the current process requires that an operator enter the space during the gassing phase, which is considered to place the personal safety of the operator at significant risk. In the interest of continuous improvement, VECTOR is requested to explore alternative, safer methods for the gaseous decontamination process.

32. *Priority 2 finding:* VECTOR should ensure that its manuals are updated to reflect changes in policy. For example, they should be updated to reflect the fact that routine use of alcohol burners has been discontinued and they are permitted only with special dispensation if the need arises to open old samples stored in glass ampules.

5. Personnel and competence

33. VECTOR provided an extensive description of their mandatory training activities. The inspection team requested and reviewed training records, which document satisfactory achievement to meet the requirements.

34. The inspection team reviewed VECTOR's training records on use of small animals. The previous finding (25) on requirements for work with animals is now closed.

35. *Observation:* VECTOR appears to be following good training practices. Training records included details of rigorous, extensive induction and documented reports of the required annual retraining.

6. Good microbiological practices

36. VECTOR provided an overview of their comprehensive training programme and documentation, including safe work practices (e.g. instruction manual, Federal health regulations). The instruction manual reflects a commitment to good microbiological practices; however, the inspection team had

no opportunity to observe adherence to good microbiological techniques during work with variola virus, as the inspection took place during the annual shut-down of the facility.

37. *Observation:* VECTOR has documentation of good microbiological practices. The documentation on the comprehensive training programme includes safe work practices.

38. *Priority 1 finding:* The inspection team recommends that VECTOR use a method to record microbiological practices (e.g. archived CCTV records) for future inspections, so that the team can verify that they are conducted in accordance with written procedures.

7. Clothing and personal protective equipment

39. During the site inspection, VECTOR demonstrated a new policy for protective suits, and procedures for suit testing, use, maintenance, repair and replacement were discussed, including information provided by the manufacturer. VECTOR also gave details of the procedure for decontaminating the suits after use and the steps for readying them for re-use. Log books are used for signing equipment in and out and for repairs.

40. The above discussions and information closed the two findings (29 and 30) on hazards and controls associated with suits and use of gloves, respectively.

41. *Observation:* VECTOR continues to upgrade and modernize the positive pressure suits that are used, i.e. with new face shields with better visibility and new cuffs.

42. *Priority 2 finding:* The inspection team recommends that a better process be used to document suit issues such as tears occurring during use (versus during cleaning and transport).

8. Human factors

43. Management of risks due to human factors for people who work in or maintain the facility was discussed. Details of hiring practices were provided; they include reviews of mental status, criminal records and psychological checks. Medical pre-employment and regular check-up requirements were discussed; these include vaccination requirements, mental stability reviews, reliability assessment and the trainability of employees.

44. The inspection team had no concern about the practices presented.

9. Health care

45. VECTOR gave an overview of the health care policy in place, including routine annual medical examinations and daily health checks for workers and staff associated with the variola programme. These were found to represent good practices. Employees working with variola virus are vaccinated every three years, and all others are vaccinated every five years. Titres are checked after every vaccination and subsequently every year. After each entry, personnel are quarantined for 21 days, when they are not allowed to travel for longer than one day outside Novosibirsk.

46. The inspection team had the opportunity to visit the new temporary hospital that makes it possible to accommodate the VECTOR staff conducting work with variola virus, for quarantine or treatment.. The permanent hospital is under reconstruction and should be finished in 2015.

47. The previous inspection noted concern with the isolation area. This finding (34) is now closed, as the space has been decommissioned.

48. *Observation:* VECTOR is clearly committed to vaccinating its staff and, as an example of good practice, also monitors their antibody titres annually. Employees' health is monitored closely, including twice-daily temperature checks and medical follow-up procedures in case of potential exposure, including differential diagnosis to rule out smallpox.

10. Emergency response and contingency planning

49. The inspection team was given an overview of emergency management procedures, including building system contingencies (e.g. back-up power), emergency plan exercises and training.

50. The previous inspection report recommended that a risk assessment be conducted on how animal work might affect emergency scenarios. This risk assessment has been completed, and this finding (36) is now closed.

51. *Observation:* VECTOR has procedures for emergency planning and accident rehearsals, which were outlined in documents provided to the inspection team. Both external and internal fire brigades will respond to fires; they are familiar with the buildings, and all the personnel have been vaccinated.

11. Accident and incident investigation

52. No accidents or incidents were reported during the period since the previous WHO inspection. The procedure for accident and incident investigation is prescribed by an executive order of the Ministry of Labour and Social Development.

53. As part of VECTOR's extensive mandatory training, personnel undergo theoretical and practical instruction in accident prevention and response. VECTOR has introduced an internal reporting system that includes written notification to the biosafety compliance committee. Internal inspections are conducted twice a year, and the Biosafety Department visits the facility each month. The recommendation (38) of the previous inspection is now closed.

54. *Observation:* VECTOR follows a detailed, prescriptive reporting system that is defined in both Federal and institutional documents. The VECTOR policies clearly indicate that its staff can report accidents and incidents without fear of recrimination.

12. Facility physical requirements

55. The WHO team noted the dedication and competence of the engineering and technical support staff.

56. *Priority 2 finding:* The inspection team recommends that long-term physical facility and its life cycle management be given the highest priority with replacement or modernization of the facility in sight. An updated biocontainment facility would position VECTOR well to support diverse high-biocontainment research programmes, regardless of any decision on destruction of variola virus. The plans should include consideration of updated containment barrier decontamination systems. If VECTOR considers that its research requires use of non-human primate models, there will be a need to upgrade the vivarium spaces, carry out a risk assessment, train the personnel and install appropriate equipment accordingly.

57. The previous recommendation that the arrangements in unused laboratories in the containment suite be improved for easier cleaning has been acted upon. Generally, a good standard of surface finish and cleanliness was observed throughout the biocontainment facility. The unused equipment was sealed to allow easy surface decontamination, and the previous finding (40) is closed.

13. Equipment and maintenance

58. The dedicated maintenance staff, who are available 24 hours a day and who met with the inspection team, are highly engaged and strongly motivated.

59. *Priority 2 finding:* The inspection team recommends that equipment to be used inside the biological safety cabinet be chosen to minimize aerosol production and interference with air currents. If the class III biological safety cabinet is to be used in the future, it should be refurbished and repaired to ensure that it provides appropriate biocontainment. The inspection team recommends that VECTOR upgrade various small pieces of laboratory equipment, such as centrifuges, to take advantage of improved purpose-designed biosafety features such as a sealed rotor or bucket.

60. *Priority 1 finding:* The inspection team recommends timely decommissioning and removal of all equipment that is not required for laboratory activities as a general rule to be implemented in high containment facilities, including decommissioned components of the ventilation plant and effluent plant, unless VECTOR could demonstrate that there is no compromise to safe work, including airflow disturbance, at the facility owing to this unnecessary equipment.

61. The self-assessment report and discussions closed the previous finding (42) on the need for an adequate cleaning and maintenance regime for unused areas and equipment.

14. Decontamination, disinfection and sterilization

62. VECTOR has established rigorous procedures for decontaminating its facilities. The regime for ensuring that disinfectants are used at a suitable concentration provides a robust audit trail and was considered a best practice. This discussion closed the previous finding (44).

63. *Priority 2 finding:* The inspection team remarked that the criteria for passing or failing the tests of concentrations of the disinfectants should be made more explicit, including a clear, documented procedure for adjusting the concentration and determining the reasons for non-conformity.

64. *Priority 1 finding:* The inspection team was informed about material flows across the containment barrier, including protective suits, sample material and low-technology tools to transfer scientific data out of containment. The practice for data transfer relies on barrier disinfection for decontamination. It is recommended that data preferably be transferred electronically (with scanners, photos or existing systems such as video cameras) to minimize the human factors in chemical decontamination and barrier fumigation.

15. Transport procedures

65. VECTOR confirmed that there were no shipments of live variola virus out of the facility during the reporting phase, and no live variola virus or DNA is stored in the containment area.

66. *Observation:* VECTOR has established detailed instructions for the packaging, monitoring and recording of material transfers.

67. *Priority 2 finding:* The inspection team recommends that a system or a second layer of containment be used to ensure that no biological materials are dispersed should cages be dropped during transfer between the rooms in the facility. The finding in the previous report (46) is ongoing.

16. Security

68. VECTOR provided an extensive overview of its security systems, which reflect coordinated security activities conducted jointly by VECTOR and employees of the Ministry of the Interior. These systems are designed to protect against risks such as unauthorized entry, terrorism, theft, misuse of materials, explosions, natural and human accidents and interpersonal conflict.

69. *Observation:* VECTOR manages an extensive system for ensuring the physical security of the laboratories, the surrounding spaces and the people who work on site. There is an effective system for securing the archival stocks as well as for protecting sensitive information and data.

OVERALL CONCLUSIONS

70. In comparison with the inspection in 2012, the WHO team found that improvements had been made and that the recommendations in the previous report had been largely addressed. The efforts and commitment of the VECTOR management and its staff to ensuring safe, secure work 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.

71. At the time of the inspection, VECTOR had no immediate reason for working with larger animals and recognized that further work on protocols and facilities would be required before they could further pursue this type of study.

72. 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.

73. 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 VECTOR 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

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