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

EXECUTIVE SUMMARY

There are currently two WHO Collaborating Centre repositories that work with smallpox virus; one is situated at the Centers for Disease Control and Prevention (CDC) in Atlanta, USA and the other at the State Research Center of Virology and Biotechnology (VECTOR) in Novosibirsk, Russian Federation.

The CDC Poxvirus Program moved into a new laboratory suite in 2009. The new laboratory is part of a high containment complex, which also houses other adjacent Biosafety Level 4 (BSL4) and Biosafety Level 3 (BSL3) laboratories.

The inspection was carried out over four days with feedback on the fifth day and consisted of group discussions, review of documentary evidence as well as inspections of the facilities and installations. At the time of the inspection the laboratory was decommissioned for maintenance.

The WHO team observed many areas of good practice during the inspection. However, a number of findings were identified and observations made for CDC's consideration. It is the responsibility of CDC to assess and implement associated actions required to address the issues raised.

The facilities can be considered to have an acceptable level of biosafety and laboratory biosecurity for variola virus research and storage. It is requested that CDC propose an action plan describing actions and timelines to rapidly address findings.

INSPECTION PROGRAMME

1. World Health Assembly resolution WHA60.1 (2007) mandates WHO to inspect these two centres every two years to ensure that 'the conditions of storage of the virus, and that the research done in the laboratories meet the highest requirements of biosafety and biosecurity'.

In addition, WHA60.1 requests that inspection-mission reports be made available for public information after appropriate scientific and security redaction.

2. In agreement with CDC and VECTOR the inspection protocol used in 2009 was used again for the inspections of 2012. The protocol is based on the publication of the international Laboratory Biorisk Management Standard, which is a consensus Workshop Agreement registered with the European Committee for Standardization (CEN) CWA 15793 (2008).

3. This inspection follows the inspection visit of March 2009. The report of the 2009 visit is available at http://www.who.int/csr/disease/smallpox/Report_2009_CDC_WHO_Inspection.pdf.

4. A new high containment laboratory (HCL) for work with variola virus has been operational since 2009. This is the only laboratory at CDC where work with live variola virus is allowed. Storage is restricted to this laboratory and one secure repository where no work with the virus is allowed. The previous laboratory has been decommissioned and is no longer operational. According to the information provided, CDC's National Select Agent Program has approved the decommissioning as completed. There are no plans to use the old facility again in the foreseeable future by CDC's Poxvirus and Rabies Branch for work with variola virus.

5. The inspection took place over four days, with a presentation and discussion of the findings on the fifth. Both CDC staff and the WHO team underlined the serious responsibility they attached to ensuring that conditions of storage of the virus and of research conducted in the laboratories continue to meet the highest requirements for biosafety and biosecurity.

6. In the introductory session on the first morning, CDC's National Select Agent Program gave an overview of U.S. Select Agent Regulations and inspection programme that applies to all work on live variola virus. CDC also presented the follow-up actions based on the previous recommendations from 2009.

7. The WHO team reported that a meeting with WHO and representatives of CDC and VECTOR had taken place in Oslo, Norway, between 31 January and 2 February 2012 to review the process for the biosafety inspection visits of the two smallpox repositories. During that meeting agreement was reached on a variety of issues, including the inspection team composition, the draft agenda for the visits, the desire to inspect the facilities when they were accessible to all team members and not in active use to permit evaluation of the laboratory facilities, and how the findings and report would be presented (i.e. a close-out session on the last day of the visit, followed by a written narrative report). The role of representatives from the repository not being inspected (in this case VECTOR) was identified by the WHO Office of the Legal Counsel to be the one of observers. Observers were able to attend interviews and site tours during the visit, but not discussions regarding findings and key observations, nor were they present at the close-out meeting.

8. The WHO team once again adopted the assessment approach first used during the 2009 inspection visits. The instrument addresses 16 elements relating to laboratory biorisk management. As in 2009, the inspection process consisted of discussions and interviews with key stakeholders, record checks, programme verification, and site inspections. Key findings

(areas of nonconformity to CWA 15793) and observations (areas that could benefit from improvement and may become a finding if not addressed before the next inspection visit) were presented for each element on the last day of the visit.

9. Discussions on element 1 (Biorisk Management System) were held in a plenary session on the afternoon of the first day. On the second and third day, the team was split into two rotating WHO-led sub-teams for group discussions on all other individual elements of the assessment protocol. The five WHO team members held closed team discussions on findings over lunch, and reconvened for further team discussions before the end of the second and third day. A brief wrap up session for questions and clarifying comments was held at the end of the second and third day.

10. The fourth day was devoted to visits by the WHO team members to several facilities including the high containment laboratory (HCL) and associated animal rooms, the heating ventilation and air-conditioning spaces, the waste treatment plant, the vault (i.e. the secure liquid nitrogen storage facility), the entry door to the gamma irradiation room, the external emergency care facility (designated to support CDC and accept suspected and confirmed laboratory acquired smallpox cases for emergency care), and the internal CDC clinic.

11. On the afternoon of the fifth day, the findings were presented to CDC staff to confirm the WHO team's understanding of initial findings with an opportunity to review, discuss and clarify any outstanding issues. Additional review and clarifying remarks occurred later by conference call.

12. The following sections describe the key findings identified by the assessment team, together with observations providing opportunities for improvement as well as areas considered to represent good practice. The structure of this report follows the 16 management elements addressed within CEN CWA 15793.

13. While a good cross-section of individuals was interviewed, it is emphasized that this was a sample of the organization and activities.

14. The inspection of the laboratory was planned for a time after the laboratory had been shut down and decontaminated to allow for annual maintenance. This provided an opportunity to visit areas that would normally be difficult to access when live virus was being handled. No actual work with variola virus was being conducted at the time of the visit. At the time of the next inspection, the opportunity to observe actual work activities when the laboratory is 'hot' will be planned with CDC.

15. In response to the inspection visit and the report, CDC is requested to propose an action plan describing actions and timelines to address findings within 30 days of receipt of the final report.

16. In conclusion, the WHO team appreciates the open and constructive attitude of CDC staff engaged in the inspection.

APPLICATION OF THE ASSESSMENT INSTRUMENT

1. Biorisk management system

17. Finding – Continue moves towards adoption of formal management system approaches relating to biorisk management

Although there are several areas highlighted in this report where progress towards the formalization of a biorisk management system at CDC have been noted, opportunities for further development of a biorisk management system were also identified. Since 2001, CDC's Office of Safety, Health and Environment (OSHE) has had a policy on adopting a management systems approach, using the principles of ISO 14001. It was the view of the WHO inspection team that applying such an approach to the work with variola virus would result in tangible enhancements through a more systematic approach to biosafety and biosecurity in several areas, including document control, enhanced internal audit / inspection activities, and formal tracking and close out of action items (see below for specific examples). Continuing the development of the biorisk management system currently in place, adopting principles from management system standards is therefore strongly encouraged.

18. Finding – Continue improvements to the variola biosafety manual and consider potential for moving to an electronic document control system

The biosafety manual (*High Containment Laboratory Manual*) relating to the work with variola virus was found to have improved since the 2009 inspection visit. However, the manual could be further strengthened by the inclusion of more SOPs describing laboratory operations, for example more detailed procedures for decontamination processes between animal rooms and the main laboratory and testing procedures for suits and air pressure control valves. A better process for controlling change implementation should also be considered (e.g. different vaccination frequencies were present in the manual than those reported elsewhere). The manual remains in paper form and challenges were reported in maintaining this large and somewhat unwieldy document. It is therefore recommended that consideration be given to the introduction of an electronic system to support document management, which currently presents a significant burden and challenge to the Poxvirus Program in maintaining an up-to-date and comprehensive document set.

19. Finding – Formally address biorisk issues through target setting and reporting mechanisms across organisation

Although the prominence of biosafety and biosecurity had been enhanced since the 2009 visit through reinforcement of the need to comply with all relevant regulations and legal requirements by formal sign off by researchers, the setting of individual and group targets and objectives in relation to biorisk management could be further strengthened. Examples of where specific biosafety and biosecurity objectives could be reflected in job performance plans include actions resulting from emergency exercises and close out

activities from the WHO visits. These areas are already being discussed within CDC, and moves towards the formalization of such initiatives, are strongly encouraged.

20. Finding – Ensure that formal mechanisms are introduced for tracking and close-out of actions, including recommendations from previous WHO inspection visits

Although there are good examples of improvement initiatives and monitoring mechanisms (e.g. through the High Containment Laboratory Operating Group (HOG)), no formal mechanism was presented to ensure the tracking and close out of action items. It is therefore recommended that the need for such mechanisms be reviewed and strengthened to ensure recommendations from areas including emergency exercises and issues identified by the HOG are adequately addressed to identify ownership, define timelines and monitor progress. Recommendations from WHO inspection visits should also be incorporated into such a system to ensure satisfactory close-out and communication of measures set in place both within the organization and to WHO.

2. Risk assessment

21. The *Biosafety in Microbiological and Biomedical Laboratories* (BMBL), 5th edition, 2009 recognizes risk assessment as an important responsibility for directors and principal investigators of microbiological laboratories, as a process to identify the hazardous characteristics of a known infectious agent, the activities that can result in a person's exposure to an agent, the likelihood that such exposure will cause a laboratory acquired infection, and the probable consequences of such an infection. The risk assessment process is essential for the determination of appropriate mitigation measures and controls necessary to ensure safe and secure working conditions.

22. Finding – 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

A number of validation studies to support risk assessments were presented in the course of the inspection, e.g. heat inactivation kinetics of variola virus under different conditions. However, the WHO team noted that there is no agreed format or methodology for recording and documenting risk assessments. In 2009 CDC was working on the development of a software system to perform risk assessments, however, the program did not meet the requirements and development was not continued. The acquisition of a new program (MEDGATE) is in progress. CDC agreed with the WHO team that the nature and approaches of the assessments presented could be further improved and this desire to further develop and apply risk-based thinking and methodologies is commended. In this regard, the close cooperation and engagement of OSHE and other specialist groups within CDC in supporting the Poxvirus Program in the development and roll out of risk assessment approaches is strongly encouraged.

3. Pathogen and toxin inventory and information

23. As noted in 2009, CDC has established an electronic inventory database and associated systems for identification, for accounting and information tracking of all materials containing live virus. The WHO inspection team also noted that the previous request to minimize volumes and concentrations of working stocks had been addressed through a specific SOP.

24. Observation – Review measures in place for control of inventory and information relating to genomic DNA

Variola virus genomic DNA is transferred to a lower containment laboratory (BSL2) where it is handled and stored; this laboratory is also under the supervision of the Poxvirus and Rabies Branch. Although security measures are in place, questions were raised by the WHO inspection team as to the risk associated with this DNA, and associated expectations on security and other controls which should be applied. This issue was considered to at least somewhat fall outside the remit of the WHO inspection team since it related to the authorizations to conduct research and the conditions that should apply, an issue that falls under the responsibility of the WHO Advisory Committee on Variola Virus Research. Although it is accepted that variola virus DNA may warrant a lower level of control than that applied to live virus stocks, the WHO inspection team recommended that a review be conducted by CDC to ensure that material is stored securely given its nature.

4. General safety

25. Finding – Consider revisiting the two person rule policy as part of the move towards more structured and systematic risk assessments

The issue of lone working and the two person rule was reported to have been discussed at the highest levels within CDC. The policy at CDC remains to allow, at certain times, staff to work alone in the maximum containment laboratory, despite strong previous WHO recommendations to re-evaluate this rule. The WHO team considered that the ability of workers to have lone access to the working environment and specimens remains an issue and encouraged CDC to provide a risk assessment identifying conditions during which lone working is justified and accepted.

26. Observation – Consider a review of noise levels on HEPA housing floor and potential need for PPE

During the tour of the plant room containing the HEPA housings, the WHO team noted elevated noise levels. Although this is not a variola-specific issue, CDC may wish to assess hazards associated with this area and consider providing hearing protection and other measures routinely found in similar environments in other, similar facilities (e.g. hard hats).

5. Personnel and competency

27. The inspection team noted that since the 2009 inspection, a number of improvements had been made including the formalization of training needs and competency assessments for scientific personnel.

28. Finding – Further strengthen measures set in place to define, monitor and record competency for staff, including maintenance and other support staff.

Moves towards the development of competency assessments were commended. However, the WHO team noted that there was potential to further develop the system and address activities more specifically (e.g. defining procedures for testing gloves before and after use, and procedures for disinfecting suits and boots before leaving the animal holding rooms and the laboratory and monitoring staff's competency in carrying these out). Furthermore, as well as including additional staff within the scope of the activity (e.g. maintenance and other support staff).

6. Good microbiological technique

29. CDC uses the BMBL 5th edition to inform basic principles, guidelines and requirements for biosafety and biosecurity. Since 2009 a member of the Poxvirus Program has been appointed to support management of SOPs and other documentation, resulting in an improvement in the quality and consistency of these documents. However, as the inspection team was not witnessing any laboratory procedures due to the facility shut down, the opportunity to comment on good microbiological technique was limited.

30. Finding – Review status of animal holding/procedure rooms with regard to whether or not they constitute primary containment during non-human primate work, and if so what additional control measures may be required.

While the containment devices (bioisolators) used for the non-filtered, fenestrated non-human primate cages in the animal holding room provide a degree of isolation between different isolators, it was unclear that these would meet established primary containment requirements for operation and procedures (e.g. those pertaining to the operator protection performance of a microbiological safety cabinet or animal isolator) . It was therefore the view of the WHO inspection team that procedures conducted would result in the room effectively becoming challenged as a primary containment barrier (e.g. transfer of anaesthetized animals within the room, cage and floor cleaning activities). This issue was further emphasized since there is also no decontamination barrier between the animal room and the remainder of the laboratory. The WHO team therefore recommended that a formal risk assessment be performed to either demonstrate that the measures (physical equipment and procedures) can be arranged in such a manner as to ensure the room does not constitute primary containment, and / or that appropriate controls are in place to prevent the transfer of potentially contaminated materials (e.g. PPE, fomites) and infectious aerosols from the animal room to the main laboratory. Should the room be found to be acting as primary containment, measures to be considered should include the need for local decontamination

of PPE (e.g. additional cleaning of gloves, boots and other items) and also other issues including the potential need to pressure test the rooms and ductwork.

7. Clothing and personal protective equipment

31. Finding – Consider the need to standardize procedures for the assessment, maintenance and repair of items of PPE

An issue identified in the 2009 report was the need to test suits in a standardized way and at an appropriate frequency, but due to the nature of the suits used at CDC, it was reported that these could not be pressure tested as recommended at that time. However, the WHO team considered that a more systematic approach to the assessment of PPE should still be applied to suit testing by a more achievable method (e.g. soap bubble testing), as well as developing procedures for selection and use of adhesives when repairing suits (e.g. taking into consideration potential material compatibility issues) and formalizing the methods for monitoring gloves.

8. Human factors

32. A variety of systems and initiatives were presented to demonstrate good practice with regard to human factors at CDC. In particular, the close-knit Poxvirus Program and evidence of good team work were observed, and it was noted that the Poxvirus Program meets regularly to discuss any issues of concern. The HOG also provides an additional opportunity to voice concerns with a larger group and have these formally recorded in the minutes of the meeting. In addition an Employee Assistance Programme is in place to identify staff-related problems and provide counseling opportunities to address and resolve issues. Training is available to help alert staff of warning signs of abnormal behaviors.

33. No significant findings were identified.

9. Healthcare

34. Good practices including routine annual medical examinations are carried out for staff at CDC. The vaccination frequency has been reduced from annual to every three years, using second generation vaccines.