WHO/CDS/CSR/GAR/2003.5

WHO Advisory Committee *on* Variola Virus Research

Report of the Fourth Meeting

GENEVA, SWITZERLAND
20–21 NOVEMBER 2002

WORLD HEALTH ORGANIZATION
DEPARTMENT OF COMMUNICABLE DISEASE
SURVEILLANCE AND RESPONSE

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Contents

Summary

The WHO Advisory Committee on Variola Virus Research reviewed progress of research involving live *Variola virus*. Considerable progress has been made during the past year but it is clear that further high priority research is still necessary. Significant advances have been made in the characterization of the *Variola virus* strains held in each repository and in the methodologies associated with virus detection and smallpox diagnosis. Work on the further refinement of the non-human primate model of smallpox is proceeding. This model is being used to assess existing antiviral compounds and there is a drug discovery programme underway. The Committee made the following recommendations:

- Inventory systems across both repositories should be standardized and improved. These inventories should be shared between the two repositories and the information reported in both hard copy and electronic formats to WHO at least once each year (paragraph 2.3).

- Records on material used for work in progress should be available for inspection and audit. The volumes of live virus suspensions generated as a result of this work should be kept to the minimum needed to successfully complete the agreed studies (paragraph 2.3).

- Where possible, information on the origin, biological properties, passage history and other characteristics of the material held in each repository should be included as part of the inventory. WHO agreed to seek information from archival records about the derivation of some of the isolates held in each collection (paragraph 2.4).

- Isolates for which there is no scientific justification for retention (particularly the chimeric and non-variola viruses held in the Centers for Disease Control and Prevention (CDC) repository) should be destroyed after informing the original donating countries of this intention (paragraph 2.4).

- Further consideration should be given to sequence analyses on additional material derived from authenticated clinical material without prior cloning (paragraph 3.3).

- Further work should be done to refine the primate model of human smallpox to facilitate its better use in assessments of candidate vaccines and antiviral agents (paragraph 7.3).

- A technical panel, containing relevant safety experts, should be convened to consider and revise the existing guidelines on the simultaneous handling of different orthopoxvirus strains with *Variola virus* (paragraph 2.5).

- This technical panel should also be charged with developing appropriate guidance on the supply of cloned DNA fragments, taking into account advances that have been made in oligonucleotide synthesis, and the possibility to modify DNA fragments of other orthopoxviruses by site-directed mutagenesis to produce the corresponding *Variola virus* gene sequence (paragraphs 5.4 and 9.4).

- Laboratories conducting approved research should produce written annual progress reports that can be disseminated to the wider scientific community in due course. Wherever possible, this research should be published in the open peer-reviewed literature (paragraph 9.5).

1. Introduction

1.1 Dr David Heymann, Executive Director, WHO Programme on Communicable Diseases welcomed participants to the meeting and asked the Committee to review progress on research using live *Variola virus* that has been conducted since its last meeting. He reminded Committee members that they had been charged with determining what research, if any, must be carried out in order to reach global consensus on the timing for the destruction of existing *Variola virus* stocks and advise WHO accordingly.

1.2 Dr Peter Greenaway was appointed Chairman and Dr Robert Drillien was appointed Rapporteur. The meeting agenda is given in Annex 1 and the meeting participants are listed in Annex 2. The meeting heard presentations from scientists from the United States of America, the United Kingdom of Great Britain and Northern Ireland and the Russian Federation who were directly involved in WHO approved research that required access to stocks of live variola viruses.

2. Update on *Variola virus* strains held in the two repositories

2.1 The VECTOR laboratory in Koltsovo, Russian Federation, reminded the Committee that their collection contains 120 samples of *Variola virus* either as passaged virus or as primary clinical specimens from various geographic areas. Some 55 isolates have been selected for further analysis. This has involved viability studies in tissue cultures or chick embryos, biological characterization and genome analysis. Of the 39 isolates studied so far only 29 were shown to be viable. DNA has been isolated from the two non-viable isolates.

2.2 The CDC laboratory in Atlanta reported progress on their analysis of a collection containing 451 isolates. It was noted that a number of these isolates are not *Variola virus* but rather *Monkeypox virus, Camelpox virus* or recombinants between *Variola virus* and other orthopoxviruses. The geographic origin and year of isolation are known for some 229 isolates. Forty-six out of the 50 isolates selected for further study on the basis of year of isolation, region of isolation, passage history and clinical information available were subsequently shown to be viable.

2.3 During these talks it became clear that systems were needed for the better audit of isolates contained within both repositories. It was therefore recommended that inventory systems across both repositories should be standardized and improved, that these inventories should be shared with each other and reported in both hard copy and electronic formats to WHO at least once each year. It was further recommended that records on material used for work in progress should be available for inspection and audit. Some members of the Committee expressed their concerns about the volumes of live virus suspensions being generated as a result of this work. It was agreed that these volumes should be kept to the minimum needed to successfully complete the agreed studies being conducted within the framework of the Committee's recommendations.

2.4 It was recommended that, where possible, information on the origin, biological properties, passage history and other characteristics of the material held in each repository should be included as part of the inventory. WHO agreed to seek information from archival records about the derivation of some of the isolates held in each collection and then make this information available to both CDC and VECTOR. It was also recommended that isolates for which there was no scientific justification for retention (particularly the chimeric and

non-variola viruses held in the CDC repository) should be destroyed after informing the original donating countries of this intention.

2.5 Finally, the question was raised whether work involving other orthopoxviruses should be conducted simultaneously with *Variola virus* strains in the same laboratory. The Global Commission for the Certification of Smallpox Eradication recommended in 1979 that this should not occur. The Committee agreed that this recommendation should be revisited given that the requirements for handling live *Variola virus* have now changed. It recommended that a technical panel, containing relevant safety experts, should be convened to consider the implications and to develop revised guidance.

3. Sequence analysis of *Variola virus* DNA

3.1 The results of DNA sequence analyses on various *Variola virus* strains were reviewed. A total of 10 full-length genomic sequences are now available. Detailed information on the heterogeneity of the *Variola virus* genome sequences analysed so far was presented and the sequence variation of the isolates was described and discussed. CDC plans to sequence at least three more complete genomes. Work at VECTOR has been more focused on obtaining data on a limited number of variable genes from a large number of isolates.

3.2 Sequencing of the genome and of individual genes and analyses of restriction fragment length polymorphisms, have enabled the establishment of phylogenetic relationships of various isolates and further understanding of the extent of the genomic diversity represented by the collections of *Variola virus* specimens in the two repositories. During these analyses it became evident that different case fatality rates in smallpox outbreaks do not correlate with particular sequence characteristics of virus isolates, which is in agreement with historical data showing that the percentage of fatal smallpox in an unvaccinated population was due to host-related factors. It was also noted that nucleotide sequence analyses have potential use in forensic testing for identifying strains and their origins in the case of a deliberate release of *Variola virus.*

3.3 The results obtained so far with single genes show no sequence variation between material from primary scab isolates or after two passages of the same samples. The Committee recommended that further consideration should be given to sequence analyses on additional material derived from authenticated clinical material and without prior cloning.

3.4 The creation of a validated and certified library of cloned *Variola virus* DNA fragments representing the virtually complete genome of two *Variola virus* strains was described and similar work using five additional strains is planned. The Committee acknowledged that this would provide material for the long-term preservation of *Variola virus* genomes but questioned whether the procedure would provide as authentic a representation of a strain as would PCR amplification of viral DNA fragments.

4 Current status of PCR and extended PCR/RFLP analysis of orthopoxvirus DNA

4.1 PCR and extended PCR-RFLP analyses on 24 cell culture isolates and 8 scab samples is in progress at VECTOR with a view to use these procedures to characterize different strains or isolates with respect to gene-dependent microheterogeneities. A number of dendograms have been constructed and this has revealed surprising variations between isolates from the same outbreak.

4.2 Similar work has been done at CDC using a capillary electrophoresis RFLP method as an alternative to gel electrophoresis techniques. This has proved to be a very sensitive method, which detects more polymorphisms than other technologies and which can be readily automated. Despite these impressive advances, it was thought that the pace of progress in DNA sequencing could circumvent the usefulness of this technology in the future.

5. Progress in the development of PCR-based diagnostic assays

5.1 A number of variations of the PCR technique have been developed to specifically detect *Variola virus* in samples containing minute amounts of DNA. The CDC and USAMRIID have begun to develop real-time PCR assays. These are based on TaqMAN chemistry and target several genomic regions. One procedure, using a two step assay, can differentiate *Variola virus* from other orthopoxviruses that infect humans. This procedure has undergone an extensive evaluation using a large nucleic acid panel derived from *Variola virus*, other orthopoxviruses and infectious agents that cause rashes resembling smallpox.

5.2 The technology is considered sensitive enough to detect as few as 50 copies of the *Variola virus* genome in specimens obtained during the prodromal period of infection. It may also be adaptable for use in the analysis of *Monkeypox virus* infections. The use of such procedures for routine sample screening has, however, shown some infidelity (approximately 1%) which may be mitigated by using additional gene targets and complementary screening methodologies.

5.3 VECTOR described the development of a multiplex PCR system capable of species–specific differentiation of orthopoxviruses. Complementary work on the development of an ARMS assay at DSTL in the United Kingdom was also discussed. It was noted that the inclusion of mismatch primers in the ARMS assay has proved to be useful for enhancing species specific detection.

5.4 The Committee encouraged all laboratories involved in this work to share the new PCR-based detection methods with the international community as soon as possible. It was recognized that the validation of these techniques outside of CDC and VECTOR could present problems due to the lack of availability of short pieces of cloned *Variola virus* DNA fragments. This may require a reconsideration of the current guidelines covering the general supply of this material. The Committee recommended that the proposed technical panel (paragraph 2.5) should be charged with developing appropriate guidance, taking into account advances that have been made in the technologies associated with nucleotide synthesis.

6. Progress in the development of serological assays

6.1 Several methods for the detection of *Variola virus* antigens were described. So far, polyclonal antibody capture assays for the detection of *Variola virus* have shown limited sensitivity and are not species-specific. Difficulties in the production of *Variola virus*-specific monoclonal antibodies have so far prevented developing a satisfactory way around this problem. Inconsistencies in the detection of all *Variola virus* isolates available were experienced when genus-specific monoclonal antibodies were used.

6.2 The Committee considered it unlikely that such serological assays would ultimately reach the sensitivity displayed by PCR methods. The utility of this technology, particularly for the early diagnosis of a *Variola virus* infection, is therefore likely to be limited. Nevertheless, it was felt that a number of useful reagents were likely to be developed.

7. Update on animal model developments

7.1 The current status of the cynomolgus monkey model for *Variola virus* infection was described. Recent experiments have demonstrated the ability of variola strains India and Harper to lethally infect monkeys at doses of 10^9 PFU/animal after intravenous inoculation. Doses of 10^8 PFU/animal were found to be lethal for only a fraction of the animals and they resulted in a slightly delayed onset of symptoms that may be more appropriate for testing of vaccines or drugs.

7.2 The use of high titer infectious doses in this model results in the bypassing of the normal prodromal stage in infected animals and direct onset of the viraemic stage. Infected animals invariably die of a disease that resembles haemorrhagic smallpox. An extensive characterization of the biological parameters associated with this animal model was reported.

7.3 The developed model was not considered ideal due to the high doses needed to achieve disease and the lack of general morbidity with consequent recovery. The Committee recommended that further work should be done to refine the model to facilitate its better deployment in assessments of candidate vaccines and antiviral agents.

8. Review of antiviral candidate drugs

8.1 Considerable effort is underway to identify new compounds active against *Variola virus* both in public institutions and private companies. VECTOR described the screening of 2432 compounds for *Variola virus* inhibitory activity. Six new compounds have been identified which will now be tested in animal models. Similar drug discovery research is also under way in both the United Kingdom of Great Britain and Northern Ireland and the United States of America where a total of some 40 lead compounds with promising properties have been identified.

8.2 Further research at USAMRIID on cidofovir was described. In the current primate model this drug protected monkeys when given 24 hours before infection but failed to protect when administered 12 hours post infection. These results may be explained by the severity of the challenge infection. Data from mouse experiments using *Cowpox virus* and *Vaccinia virus* indicate that the effectiveness of cidofovir is highly dependent on the dose of challenge virus and that post-infection protection could be conferred only when low doses were used to initiate infection.

8.3 The Committee recognized that cidofovir was not the drug of choice because of its route of administration and nephrotoxicity. It therefore welcomed the results obtained on three pro-drug derivatives of cidofovir that can be orally administered. These have been shown to be less toxic than cidofovir and greater plasma concentrations can be achieved. The drugs are effective in animals (mice) infected with cowpox. It will be another 6 months before these drugs can be tested in the non-human primate model of smallpox.

9. General discussion

9.1 Four vaccine development programmes were referred to during the general discussion following these scientific reports. First, the United Kingdom reported on work aimed at developing second generation subunit vaccines; this was still at the stage of identifying suitable protective antigens. Second, both the United Kingdom and the United States reported some work on assessing modified Vaccinia virus Ankara (MVA) as a candidate live attenuated vaccine. Third, the United States has some ongoing work on the development of DNA vaccines using coding sequences of four antigens; this work is still at an early stage. Finally, the Russian Federation is experimenting with multivalent vaccines based on attenuated *Vaccinia virus* vectors.

The Russian delegation also disseminated among the Committee members a Program of Research and Development of Countermeasures to Protect the Russian Federation Population from Attacks Involving Deliberate Use of Variola Virus (2003-2007) and called for collaboration with scientists and agencies from WHO member countries.

9.2 There was then some discussion of research on the use of passive immunotherapy following the administration of live *Vaccinia virus* vaccines. It was recognized that there was no strong evidence for the beneficial use of vaccinia immune globulin (VIG). Nevertheless, there was some ongoing work on the humanization of mouse monoclonal antibodies that could be used for this purpose. In addition, the United States indicated that work on humanizing the immune system of cows was in progress with a view to using these transgenic animals to produce VIG.

9.3 A number of general safety issues were then discussed, some of which have been referred to earlier. These included the possibility of distributing short fragments of *Variola virus* DNA to validate PCR diagnostic procedures, site-directed mutagenesis of *Vaccinia virus* DNA to make it *Variola virus*-like, the insertion of foreign genes into *Variola virus* and the simultaneous use of *Variola virus* and other orthopoxviruses in high containment suites. All of these issues were precluded if strict interpretations of existing guidelines were applied.

9.4 The Committee recognized that these interpretations were now open to challenge because of the technological advances that have been made since the existing guidelines were first introduced. The Committee felt that it did not have the expertise or competence to offer advice to WHO on these matters at this stage. It was thought that the technical panel referred to previously should be urgently convened to consider these issues and develop appropriate guidance for WHO to disseminate.

9.5 Finally, the Committee was encouraged by the considerable progress being made in research dealing with *Variola virus* and it recommended that this effort should be continued. Laboratories conducting this approved research are requested to produce written annual progress reports that can be disseminated to the wider scientific community in due course. The Committee further recommended that all research be published in the open peer-reviewed literature.

Annex 1: Agenda

20 November 2002

9:00 – 9:15	Welcome, Purpose of Meeting
9:15 – 10:00	Update of variola virus strains in collection, results of viability studies Presentation by Professor Sergei N. Shchelkunov and Dr Inger Damon
10:00 – 10:30	COFFEE BREAK
10:30 – 11:30	Sequence analysis of *Variola virus* DNA Presentation by Dr J. Esposito and Professor Sergei N. Shchelkunov: "Creation of collections of hybrid plasmids containing *Variola virus* DNA fragments"
11:30 – 12:30	Current status of PCR and extended PCR/RFLP analysis of orthopoxvirus DNA Presentation by Professor Sergei N. Shchelkunov and Dr Inger Damon: Capillary-electrophoresis RFLP (CRFLP): "A new method for poxvirus fingerprinting"
12:30 – 14:00	LUNCH
14:00 – 15:15	Progress in development of PCR-based diagnostic assays Presentation by Dr Inger Damon: "Updates on diagnostic development and use" Presentation by Dr Peter B. Jahrling: "Design and validation of two variola virus TaqMan Assays" Presentation by Professor Sergei N. Shchelkunov and Dr David Ulaeto: "Development of multiplex PCR analysis for species-specific differentiation of orthopoxviruses"
15:15 – 15:30	Progress in development of serological assays Presentation by Dr David Ulaeto
15:30 – 16:00	COFFEE BREAK
16:00 – 17:00	Update of animal model developments Presentation by Dr Peter B. Jahrling: "Lethal infection of primates as a model for human smallpox"

21 November 2002

8:30 – 10:00 Review of antiviral candidate drugs

Presentation by Dr Evgeny Belanov: "Search for anti-virals active against orthopoxviruses pathogenic for humans"

Presentation by Dr John W. Huggins: "Therapy of smallpox: current status of cidofovir (Vistide) and progress on oral prodrugs"

10.00 – 10.30 COFFEE BREAK

10.30 – 11.00 Report from the Secretariat

11.00 – 12.00 General Discussion

12.00 – 13.30 LUNCH

13.30 – 15.00 General Discussion (cont.) and preparation of draft recommendations

15.00 – 15.30 COFFEE BREAK

15.30 – 17.00 Consensus on recommendations

Annex 2: List of participants

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