GLOBAL HEALTH SECURITY

EPIDEMIC ALERT & RESPONSE

WHO Advisory Committee on Variola Virus Research

Report of the Fifth Meeting

Geneva, Switzerland
4 - 5 November 2003

World Health Organization

Department of Communicable Disease Surveillance and Response

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Contents

Summary

The fifth meeting of the WHO Advisory Committee on Variola Virus Research reviewed current progress in essential research requiring access to live variola virus. Significant progress has been made during the past reporting year, particularly in the further characterization of the variola virus isolates held in the two repositories, on the development of diagnostic procedures for smallpox, and on studies of the genomic DNA diversity of variola virus. Additional progress was also reported on further refinement of the non-human primate model of smallpox and its use for assessing the efficacy of new antiviral compounds and vaccines.

The committee made the following recommendations:

- Chimeric viruses held in the Centers for Disease Control and Prevention (CDC) repository should be destroyed and removed from the inventory; this would not preclude the preparation of genomic DNA samples for subsequent archiving.

- Isolates shown to be non-viable using the procedures employed should be similarly destroyed and removed from the inventories, with DNA being isolated if considered useful for future studies.

- WHO should approach the responsible authorities of the collaborating centres to implement the recommendations concerning destruction of the virus isolates identified above.

- The virus inventories held by the two collaborating centres should be updated according to a standardized format set up in collaboration with the WHO secretariat. Progress on implementing this recommendation should be reviewed at the next meeting of the Advisory Committee.

- Non-variola virus orthopoxviruses held in the CDC repository should not appear on the inventory and should either be held separately within the BSL-4 facility or be destroyed, as recommended previously for isolates whose retention was not scientifically justified.

- Methodologies for all diagnostic assays for smallpox developed during this programme should be made available to Member States that request them.

- Additional research should be conducted to validate the current procedures for extraction of DNA from authentic clinical samples containing variola virus DNA and to validate the available diagnostic tests using material from variola virus-infected non-human primates or historical samples.

- Further work should be done using the primate model of human smallpox to facilitate the identification of candidate antiviral compounds and vaccines.

- Work on the characterization of potential antiviral lead compounds and on the development of new vaccines should be given a high priority.

- WHO should provide guidelines for assessing the quality, safety and efficacy of new generation smallpox vaccines for those Member States engaged in this important research.

- The recommendations of the technical sub-committee and the views of members of the Advisory Committee on the simultaneous handling of variola virus and other orthopoxviruses, on the genetic engineering of variola virus, on the expression of variola virus genes in other orthopoxviruses and on the distribution of variola virus DNA should be referred to WHO's Biosafety Advisory Group and, subsequently, to the Ad Hoc Committee on Orthopoxvirus Infections for final adjudication.

1. Introduction and report of the Secretariat

1.1 Dr Guénaël Rodier, WHO Director, Communicable Disease Surveillance and Response (CSR), welcomed participants to the meeting. He indicated that the purpose of the meeting was to review current progress on research using live variola virus, to comment on the essential research required in advance of further consideration of the destruction of all remaining known live virus stocks. Dr Peter Greenaway was appointed Chairman and Dr Robert Drillien Rapporteur.

1.2 Dr Cathy Roth then summarized the work of the WHO Advisory Committee Secretariat during the past year. A standard electronic format for recording the variola virus inventories held by the two WHO collaborating centres had been prepared and would soon be available for distribution. The information to be collected would include origin, history, virulence, titre, etc. of each of the isolates in the repositories and records on material used for work in progress. She indicated that inspections of the BSL-4 facilities within each of the two WHO collaborating centres had been completed.

1.3 A number of associated activities were then described. These included the potency testing of the smallpox vaccine reserve held by WHO (all stocks potent), the archiving of smallpox-related documents generated between 1987 and 1998 and the investigation of rumours of two possible smallpox cases (both negative). WHO had also organized workshops on the modelling of a smallpox outbreak, on virus isolation and case management, and on the laboratory validation of diagnostic assays. The Organization had also held a training course for those involved in the training of emergency responders to a smallpox outbreak and had participated in the international emergency response exercise known as "Global Mercury".

1.4 Some of these initiatives fell outside the remit of the Advisory Committee on Variola Virus Research and were more policy-related. It was therefore expected that the Ad Hoc Committee on Orthopoxvirus Infections would be reconvened to consider the policy-related initiatives and relevant recommendations of this Advisory Committee.

1.5 Dr Riccardo Wittek then described the work of the technical panel convened following the fourth meeting of this Advisory Committee. Members had been selected from the Advisory Committee on the basis of their scientific expertise and representation on national biosafety committees. The panel's draft recommendations were available for discussion later in the agenda.

2. Report and update on biosafety

2.1 Dr Nicoletta Previsani described aspects of the WHO Biosafety Programme relevant to variola virus. She indicated that the WHO Biosafety Programme had recently been joined by

the Emergency Preparedness Team. With respect to emergency preparedness, WHO had developed surveillance standards for smallpox and standard operating procedures for outbreak response procedures.

2.2 The revised regulations for the transport of infectious substances were described. These were now being considered by the international civil aviation authorities and the International Air Transport Association (IATA). The object is to seek harmonization of transport regulations between the airline and national authorities. These regulations were dependent on the categorization of infectious substances into those considered most dangerous (including variola virus) and those of low risk. A list of the agents in each category was distributed to Committee members.

2.3 During the ensuing discussion it was agreed that biosecurity, in addition to biosafety, would be an important consideration if the transportation of live variola virus were ever considered outside of an outbreak situation. It was noted that Congo 9 was the only common isolate held by the two collaborating centres and that at some point in the future the exchange of key samples might need to be contemplated. It was unclear who would be the ultimate authority to sanction such exchange if, indeed, it were ever considered practical.

3. Virus repositories

3.1 Progress reports on ongoing research with live variola virus were presented by scientists from the CDC and the Russian State Centre for Virology and Biotechnology (VECTOR) laboratories. The current variola virus stocks at CDC include 451 isolates, of which 49 have been selected for viability studies. Forty-five of these isolates could be propagated in tissue culture. Polymerase chain reaction/restriction fragment length polymorphism (PCR/RFLP) analysis of DNA samples from the 45 isolates has allowed the establishment of dendrograms that demonstrate the clustering of the isolates into clades according to the geographical origin of the viruses. Methods such as extended PCR/RFLP and capillary RFLP have been employed to identify more precisely the geographical origin of isolates of particular interest. Out of the 120 samples at VECTOR, 55 were tested for viability and 32 could be propagated. DNA from 21 isolates at VECTOR has been analysed by long PCR/RFLP analysis. This work has facilitated the construction of dendrograms that show the distribution of the isolates into three major groups (African, Asian and Alastrim virus). Analysis of Moscow isolates from the 1960 outbreak has identified polymorphic differences in the genomes of individual isolates.

3.2 The published properties of the Alastrim/rabbitpox and Harvey/cowpox chimeric viruses held within the CDC repository were described. It was noted that these viruses had not yet been destroyed, as was recommended at a previous meeting. The Committee (with one dissension) renewed the recommendation that these chimeric viruses should be destroyed and removed from the inventory; this would not preclude the preparation of genomic DNA samples for subsequent archiving. The Committee also recommended that isolates shown to be non-viable using the procedures employed should be destroyed and removed from the inventories, with DNA being isolated if this was considered useful for future studies.

3.3 The Committee recommended that WHO should approach the responsible authorities within the collaborating centres to implement the recommendations concerning the destruction of these virus isolates.

3.4 The Committee reiterated its recommendation that virus inventories be updated according to a standardized format set up in collaboration with the WHO secretariat and that progress on implementing this recommendation should be reviewed at its next meeting. It was agreed that the non-variola viruses held in the CDC repository should not appear on the inventory and should either be held separately within the BSL-4 facility or be destroyed, as recommended previously for isolates whose retention was not scientifically justified.

4. Diagnostic and detection methods

4.1 Current progress in the development of diagnostic methods for variola virus detection was reviewed. Real-time PCR methods for the identification of variola DNA that rely on the endonuclease activity of the Taq polymerase or probe hybridization using minor groove-binding proteins have been successfully employed at CDC. This method was found to provide greater sensitivity and specificity via the use of shorter probes. The CDC laboratory has also established coded DNA panels, including variola virus DNA and other orthopoxvirus DNA samples, for the evaluation of viral DNA identification assays. The Committee recommended that these methodologies be made available to all Member States that request them.

4.2 It was reported that real-time PCR assays had been successfully used during a recent monkeypox outbreak in the USA. An IgM capture assay for the detection of antibodies recognizing orthopoxvirus antigens was also used during that outbreak and found to be effective in 29 out of 33 positive cases: in the four negative cases, samples were drawn at 1, 2 and 4 days following the appearance of rash. Algorithms for conducting orthopoxvirus diagnosis in a rational manner have been developed at CDC.

4.3 Research on the development of hyphen monoclonal antibodies was reported. Although this work has not resulted in readily usable assays, strategies are under way to solve the problems encountered, particularly by combining several monoclonal antibodies.

4.4 Current developments in the diagnosis of variola virus by scientists in the United Kingdom were reported. A multiplex PCR technique that allows the differentiation of variola DNA from other orthopoxvirus DNAs has been set up.

4.5 Overall, the Committee acknowledged the very satisfactory rate of progress in the area of variola virus diagnosis and detection. It was recognized that additional work should be completed on authentic variola virus lesions from infected non-human primates or historical samples using the available diagnostic tests, and that it was essential to confirm the effectiveness of current DNA extraction procedures using such material. Furthermore, the importance of allowing outside scientists access to non-infectious variola material for validation of their diagnostic tools was stressed.

5. Sequence analysis

5.1 Extensive sequence analysis of variola virus DNA samples has been pursued. The VECTOR laboratories reported the sequencing of five genes from a wide range of orthopoxviruses, including variola virus.

This work has allowed the construction of dendrograms illustrating the close relationship between different isolates of similar origin, with the exception of cowpox virus isolates which appear to be more heterogeneous when compared with each other. Nevertheless, it was observed that there may be difficulties in establishing phylogenetic relationships using a limited number of genes.

5.2 The full-length sequences of 26 different variola virus genomes, excluding their terminal hairpin loops, were reported by CDC. A rapid sequencing method, based on the use of oligonucleotides on microchips that can facilitate confirmation of known genomes, is under development. This study has highlighted unique features of the variola virus genomes, such as the organization of the tandem repeats and the presence of poly (T) and poly (dAT) repeats. New computer software is being developed for the analysis and visualization of conservation and variation along the variola virus genome.

6. Development of an animal model of smallpox

6.1 Progress in developing the primate model of smallpox was presented by scientists from the United States Army Medical Research Institute for Infectious Diseases (USAMRIID). Previously, variola virus infection of macaques with high viral doses (10^9 PFU) administered by intravenously was shown to lead to a lethal, haemorrhagic disease that displays similarities to haemorrhagic smallpox. Further characterization of the biological parameters of the infection was reported at this meeting, and it was agreed that more work was needed on the mucosal and intratracheal routes of infection and on studies to determine whether sequential passage of variola virus in monkeys caused an increase in virus virulence. It was also agreed that further work was needed to establish the primate/monkeypox model as a surrogate model and as a bridge for vaccine licensing.

7. Development of antiviral drugs

7.1 The Committee accepted that essential research on the animal model of smallpox was needed to meet the efficacy rules for the licensing of new antiviral compounds. Antiviral treatment with cidofovir has been shown to protect monkeys against variola-induced death if given 24 hours before infection. When lower viral doses were employed (10^8 PFU) in a model more representative of authentic smallpox, cidofovir was shown to protect animals if given 2 days after infection under conditions in which control animals displayed large lesions and partial lethality.

7.2 Cidofovir has also been tested in the monkeypox virus challenge model in monkeys, which is representative of classical smallpox; the results demonstrate that it is possible to protect animals when the drug is given 24 hours before infection. It is also possible to partially protect animals when the drug is given 48 hours after infection. New oral formulations of cidofovir conjugated with lipids have shown increased potency both in vitro and in mice lethally challenged with cowpox.

7.3 In additional in silico drug discovery programmes, reviewed by scientists at USAMRIID, more than 33.5 million compounds were screened and some 48 new potential lead compounds have been identified. Studies at VECTOR have screened more than 4300

compounds. A number of promising new compounds have been identified and their antiviral properties are being studied in vitro and using the mouse/cowpox model.

8. Vaccine studies

8.1 The monkeypox challenge model has been used by scientists at the National Institutes of Health (NIH) to test the ability of a modified vaccinia virus Ankara (MVA) strain, from NIH to protect monkeys. Two doses of MVA given at 8-week intervals proved to be nearly as effective as a single dose of the conventional Dryvax smallpox vaccine. Immunization with MVA, followed by a Dryvax boost, reduced the size of the lesion produced by the latter vaccine and also induced protection against monkeypox virus challenge, although this protection was inferior to that produced by Dryvax.

8.2 The United Kingdom is supporting research on candidate subunit vaccines using the A27L, A33R and B5R gene products produced in baculovirus expression systems. The mouse model using intranasal challenge with vaccinia is being used. All this work involves using Alhydrogel adjuvants. Vaccination studies using combinations of these antigens are now in progress. Initial studies have demonstrated that DNA immunization with these genes produce virtually the same results.

8.3 Work conducted in China using an attenuated Tian Tan strain was also described briefly. This strain apparently does not replicate in human cells but can grow in chick embryo fibroblasts. A Phase 1 clinical trial using the attenuated Tian Tan strain containing HIV gene sequences is expected. This work, along with that reported by the United Kingdom, drew attention to the need for guidelines for assessing the quality, safety and efficacy of new-generation smallpox vaccines for those Member States engaged in this important research.

9. The USA monkeypox outbreak

9.1 An extensive overview of the clinical and diagnostic experience gained during the recent monkeypox outbreak in the USA was presented. Thirty-seven laboratory-confirmed human cases occurred during this outbreak: relatively few were severe and none was lethal. There were no confirmed human-to-human transmissions and some evidence indicated that previous smallpox vaccination ameliorated the disease outcome. Evidence was obtained that six individuals with no clinical symptoms had also been infected.

9.2 Preliminary work suggested that the recent cases represent infection by a distinct subspecies of a monkeypox virus previously identified in humans in several African nations. Prairie dogs were likely to have been the main animal vehicle for transmission and had probably been infected following co-location with specific imported African rodent species. Some concern was expressed over the possible creation of a North American animal reservoir for monkeypox virus. It was observed that the full range of animal species susceptible to monkeypox virus was unknown, and the pathogenesis of disease in susceptible animals was poorly understood.

10. Dissemination of research results

10.1 Dr Cathy Roth reiterated WHO's commitment to ensuring that the results of all research involving variola virus should be made widely available. Abstracts of the research presented at this meeting would eventually be published on the WHO web site. Researchers were encouraged to publish their results in the open literature subject, of course, to the prior protection of any associated intellectual property and relevant legal requirements of the Member State hosting the research programmes.

11. Recommendations from the technical subcommittee

11.1 The Advisory Committee was informed that the technical subcommittee, appointed following last year's meeting, had considered four specific issues submitted to it for scrutiny. Each issue and the associated recommendation were considered separately by the Advisory Committee.

11.2 The first issue concerned the simultaneous handling of variola virus and other orthopoxviruses within the same BSL-4 laboratory. The technical subcommittee recommended that this would not pose a significant problem provided that all infected materials were properly decontaminated or disposed of at the end of the experiment. One member of the Advisory Committee challenged this view on the grounds that it was not virologically sound.

11.3 The second issue was the generation of recombinant variola viruses expressing reporter genes, such as the gene encoding the green fluorescent protein. The technical subcommittee recommended that this should be permitted provided that there were compelling and documented reasons for generating such recombinants and that a detailed risk analysis was produced demonstrating that the marker gene would not alter the biological properties of the created recombinant virus. It also recommended that absence of mutations in the reporter gene and in the flanking variola virus DNA sequences in the insertion plasmid must be demonstrated by sequence analysis before any attempt to generate recombinant variola virus. It was subsequently recommended that all materials, as well as the stocks of recombinant variola viruses, should be destroyed as soon as possible after the relevant experimental work had been completed.

11.4 The Advisory Committee recognized that the availability of these recombinants would facilitate the screening of antiviral compounds and would therefore speed the identification of efficacious compounds.

11.5 The third issue concerned the expression of variola virus genes in other orthopoxviruses. The technical subcommittee recommended that this should be permitted provided that a detailed risk analysis had been done to demonstrate that the expression of the variola virus gene was unlikely to alter the biological properties of the orthopoxvirus vector. Additional requirements were that scientists generating and handling such recombinant viruses had had a recent smallpox vaccination, that not more than one variola virus gene was inserted into the vector, and that all experiments were performed at BSL-3 level containment. It was further recommended that BSL-2 level containment could be used if all of the above conditions were fulfilled and that highly attenuated strains such as the MVA or NYVAC strains, were used as vectors, that they had been extensively characterized and shown to be replication-defective in most mammalian cells, and that they had been demonstrated to be safe in animals.

11.6 The Advisory Committee recognized that these experiments were technologically possible and could be achieved both by the direct insertion of variola virus genes or by the insertion of gene sequences made "variola-like" by synthesis or by site-directed mutagenesis of homologous genes. It also recognized that these recombinants would speed up the completion of some of the essential research already identified. However, the recommendations of the technical subcommittee were questioned by some members of the Advisory Committee, particularly as the full scope of the issues under consideration was felt to be beyond the expertise of members of the technical subcommittee alone.

11.7 The final issue concerned the distribution and in vitro synthesis of variola virus DNA. The technical subcommittee recommended that fragments of variola virus DNA, not exceeding 500 base pairs in length, may be freely distributed between laboratories for use as positive controls in diagnostic kits. Larger fragments of variola virus DNA, not exceeding 20% of the total genome size, may be obtained from either of the two WHO collaborating centres provided that WHO grants permission for the receipt of such DNA. Finally, the technical subcommittee recommended that full-length genomic variola virus DNA may be exchanged between the two WHO collaborating centres holding variola virus. The Advisory Committee recommended, in addition, that in vitro synthesis of double-stranded DNA fragments exceeding 500 base pairs in length should not be performed without prior approval from WHO but that this restriction did not apply to microarrays, on which small oligonucleotides (<80 base pairs) are covalently bound to a matrix and which, in aggregate, may span the entire genome. The Advisory Committee accepted these recommendations with dissent being expressed by one member.

11.8 Overall the Advisory Committee accepted the recommendations of the technical subcommittee on the first and fourth issues but had significant reservations concerning the recommendations on the second and third issues. After considerable discussion, the Advisory Committee recommended that these issues and the views expressed by Committee members should be referred to WHO's Biosafety Advisory Group and, subsequently, to the reconvened Ad Hoc Committee on Orthopoxvirus Infections for final adjudication.

12. Conclusion

12.1 The Committee recognized that major progress had been made in the various areas of research reported and that no important gaps could be identified at the present time. In particular, promising developments in the field of new drug discovery and safer vaccines were reported. However, it was considered that substantial further work would be required to achieve the goals in these two areas. Thus, the Committee acknowledged the need for continued research on anti-variola drugs and safer vaccines and expressed the view that this type of research should receive adequate support in order to reach a successful conclusion in the shortest time possible.

Annex 1: Agenda

4 November 2003

9:00 – 9:15 Welcome. Purpose of meeting

9:15 – 9:30 Report of the secretariat – C. Roth, R. Wittek, R. Andraghetti

9:30 – 9:45 Report and update on biosafety – N. Previsani

9:45 – 10:30 Update on variola virus strains in collection, results of viability studies

- Inventory and update on the variola strains at the WHO Collaborating Centre – I. Damon (CDC – USA)
- Viability estimation of variola virus isolates from the Russian collection – S.N. Schelkunov (VECTOR – Russian Federation)
- Comparative restriction analysis of genomic DNAs of the variola virus strains from the Russian collection – I.V. Babkin (VECTOR – Russian Federation)

10:30 – 11:00 Tea/coffee break

11:00 – 11:30 Update and progress on virological and serological assays

- Update on diagnostic development: nucleic acid and serologic based – I. Damon (CDC – USA)
- Detection and diagnostics – D. Ulaeto (Defence Science and Technology Laboratory, Dstl-UK)

11:30 – 12:30 Sequence analysis of variola virus DNA

- Analysis of nucleotide sequences of individual orthopoxvirus genes – I.V. Babkin ("VECTOR" – Russian Federation)
- Genomic DNA diversity of variola virus – J. Esposito (CDC – USA)

12:30 – 14:00 Lunch

14:00 – 14:30 Update on animal model developments

- Proposed refinements to the variola primate model for human smallpox – P. Jahrling (USAMRIID - USA)

14:30 – 15:30 Review of antiviral candidate drugs

- Progress on the development of antiviral therapy for smallpox (and monkeypox)
  – J. Huggins (USAMRIID - USA)

15:30 – 16:00 Tea/coffee break

16:00 – 17:00 Review of antiviral candidate drugs (cont.)

- An update on screening of antivirals against orthopoxviruses, including smallpox
  – E. Belanov (VECTOR – Russian Federation)

- Medical countermeasures (vaccine/antiviral)
  – D. Ulaeto (Defence Science and Technology Laboratory, UK)

5 November 2003

9:00 – 9:30 US monkeypox experience
– I. Damon (CDC – USA)

9:30 – 10:00 Dissemination of research results

10:00 – 10:30 Tea/coffee break

10:30 – 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 Tea/coffee break

15:30 – 17:00 Consensus on recommendations

Annex 2: List of participants

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