

EPIDEMIC
ALERT &
RESPONSE

WHO Advisory Committee on Variola Virus Research

Report of the Sixth Meeting

Geneva, Switzerland
4–5 November 2004

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World Health Organization
Department of Communicable Disease
Surveillance and Response

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1. Introduction and report of the Secretariat

1.1 Dr Mike Ryan welcomed participants to the sixth meeting of the WHO Advisory Committee on Variola Virus Research. This was reiterated by Dr Cathy Roth who indicated that the purpose of the meeting was to review the progress of current essential research that depended on access to live variola virus, to advise WHO on the continuing need for this research and to consider proposed revisions to the 1994 recommendations of the Ad Hoc Committee on Orthopoxvirus Infections. Professor Geoffrey Smith was appointed Chairman and Dr Robert Drillien and Dr Peter Greenaway Rapporteurs.

1.2 Dr Daniel Lavanchy then summarized the work of the WHO Secretariat during the past year. He noted that the Ad Hoc Committee on Orthopoxvirus Infections, which advises WHO on public health perspectives, had met on 31 August and 1 September 2004 to consider two main issues.

1.3 The first item considered by the Ad Hoc Committee was a proposed operational framework for the development and management of a smallpox vaccine stockpile and strategic reserve of smallpox vaccine for use by WHO in an emergency. It was intended that this should be composed of two components – a stock of 5×10^6 doses to be held in Geneva and pledged stocks of 200×10^6 doses to be held by Member States. The operational framework governing the generation and use of these stocks was now being considered by WHO.

1.4 Second, the Ad Hoc Committee considered possible revisions to their 1994 recommendations concerning the handling of live variola virus and variola virus DNA. The conclusion was that members of the WHO Advisory Committee on Variola Virus Research were best placed to propose changes to these recommendations and advise on how any changes should be implemented.

2. Update on variola virus strains in the two virus repositories

2.1 Updates were given on the variola virus strains held in the repositories at the Russian State Centre for Research on Virology and Biotechnology (VECTOR), Koltsovo, Russian Federation and the Centers for Disease Control and Prevention, Atlanta, United States of America. Basically, there had been no change in the inventories at either repository. However, a unifying inventory system giving (where known) the derivation of each strain, the material available, virus titre and number of vials was being introduced. These inventories were compliant with the United States Regulations on Select Agents and were lodged with WHO.

2.2 The Advisory Committee was reminded that the Russian collection comprises 120 strains, including 17 primary isolates. It also holds libraries of hybrid plasmids carrying DNA fragments of the complete genomes of eight variola virus strains belonging to two epidemiological types and isolated in different geographical regions of the world. Two internal inspections had been carried out in January and June 2004 that confirmed that the repository was being adequately maintained and that the inventory corresponded to what variola virus cultures were present.

2.3 The Advisory Committee was also reminded that the United States collection contained 451 isolates. The year/date of isolation was known for 229 of these and the geographical area of isolation was known for 238 of them. A total of 49 isolates from divergent geographical origin, year of isolation and low passage number were chosen for in-depth study. Of these, 45 were shown to be viable and have been subject to restriction fragment length polymorphism (RFLP) analysis. Of these, 40 have been sequenced completely. It was noted that a number of requests had been made for the supply of DNA fragments for diagnostic purposes. These have been fulfilled.

2.4 The Advisory Committee was informed that work on the rabbitpox/variola virus chimeric viruses had been carried out to further characterize available diagnostic tests and that additional work on these viruses as well as on the cowpox/variola chimeric viruses was being contemplated before DNA could be isolated from these viruses and archived. Problems with the availability of the BSL-4 laboratory have delayed this work. The Committee maintained the view that retention of the viruses had no scientific justification and repeated the recommendation, made at its fourth and fifth meetings, that these viruses should be destroyed and their destruction recorded in the inventory.

3. Update on diagnostic assays

3.1 Dr I. Damon then presented a "Review and update on reagents and diagnostics: nucleic acids, preparing for FDA review, and monoclonal characterization". The key points were:

- quantitative and qualitative diagnostic assays based on real-time PCR were available and had been field-tested. Reagents and protocols had been refined and standardized. Validated tests had been distributed to public health laboratories;
- the sensitivity of these tests was now down to between 5 and 50 genome copies using DNA prepared from purified virus. The tests were capable of differentiating variola virus from other orthopoxviruses and distinguishing between different variola virus strains;
- IgM capture assays had been used successfully to follow the immune responses to monkeypox virus infections in the United States as well as classifying possible cases. IgM responses to monkeypox virus infection could be detected in those vaccinated previously against smallpox;
- laboratory algorithms covering febrile illness had been developed;
- monoclonal antibodies recognizing conformational epitopes to variola virus have been characterized partially and have some variola virus-specific neutralizing activity. Further analysis of a second set of monoclonal antibodies revealed that they recognize a 41 kDa protein of variola, vaccinia and camelpox viruses.

3.2 Dr H. Meyer presented a paper on the "Detection of orthopoxviruses and simultaneous identification of smallpox virus". He noted that available methods for the identification and differentiation of orthopoxviruses were based on electron microscopy, antigen and antibody detection, isolation and real-time PCR. He noted that:

- the identification of variola virus could be both rapid and specific;
- robust methodologies had been developed and published, and the reagents involved had been produced to good manufacturing practices (GMP) standards;
- tests to differentiate orthopoxvirus strains had been field-tested and these could also differentiate orthopoxvirus infections from other confounding virus infections such as Varicella-zoster virus infections.

3.3 Dr N. Tikunova described her work on the production of "Human combinatorial antibodies against orthopoxviruses". The objective here was to create a collection of recombinant human antibodies against orthopoxviruses and to select those with either genus specificity or variola virus specificity. In summary:

- initial work using a combinatorial synthetic phage display library had yielded a number of antibodies that recognized orthopoxviruses including variola virus, but none of these neutralized variola virus;
- it was decided to create a phage display library from individuals immunized with vaccinia virus;
- antibodies that can be used for orthopoxvirus differentiation and neutralization were obtained and characterized.

3.4 Dr V. Loktev presented a paper on "Cross-reactive neutralizing monoclonal antibodies to the orthopoxviruses". The key points made included:

- hyperimmune sera to different orthopoxviruses are not discriminatory as there are many cross-reactions. This provides a justification for the isolation of neutralizing monoclonal antibodies;
- rat and mouse hybridomas against ectromelia, vaccinia and monkeypox viruses have been produced, or obtained from Dr Ichihashi, and characterized;
- many of these recognize a native 14 kDa protein from variola and ectromelia viruses and may recognize a neutralizing cross-reactive epitope. Some of these were able to neutralize variola and vaccinia viruses.

4. Update on vaccines

4.1 Professor S. Shchelkunov initiated this part of the meeting by describing the "Creation of a live polyvalent vaccine against human immunodeficiency virus, hepatitis B virus, and orthopoxviruses". He noted that such a vaccine would have significant benefits for both biosecurity and public health. The candidate vaccine had been created using coding sequences for T-cell and B-cell epitopes of human immunodeficiency virus (HIV) and hepatitis B virus (HBV) proteins,

which subsequently had been inserted into vaccinia virus. The recombinants produced had the following characteristics:

- were stable in tissue culture over 10 passages;
- induced immune responses to the expected epitopes when inoculated subcutaneously and intracutaneously in BALB/c mice;
- were candidates for a live polyvalent virus vaccine.

4.2 Dr A. Sergeev presented a paper describing studies on the "Reactogenicity, safety and immunogenicity of recombinant variola and hepatitis B bivalent vaccine for oral immunization in humans". This vaccine had been developed because of the risk associated with the use of intradermal inoculations. Tablets "Revax-BT" had been produced. These were stable at -20°C for 3 years and could be administered orally (held in the mouth while dissolving). He described:

- a clinical trial in which volunteers of different ages and vaccinia immune status were immunized with different doses of vaccine at different times;
- results in which both different degrees of reactogenicity and different levels of immune responses were detected;
- difficulties in obtaining significant immune response to hepatitis B antigens;
- an optimal scheme for immunization.

4.3 Dr D. Ulaeto then outlined "UK research on medical countermeasures to smallpox". The aim of this research is to develop or provide access to effective and licensed vaccines and pharmaceutical countermeasures to smallpox. He indicated that the United Kingdom had:

- purchased vaccine stocks based on the Lister strain grown in tissue culture and had benchmarked these against existing vaccine stocks;
- observed some variation in protective efficacy of the different vaccine stocks in mice;
- undertaken studies on the efficacy of modified vaccinia virus Ankara (MVA) as a second-generation vaccine and that this had performed well in murine lethal challenge experiments;
- studied subunit vaccines based on both proteins and DNA and was investigating correlates of protection;
- collaborated with the USA in identifying antiviral agents directed against different virus-encoded functions.

5. Sequence analysis of variola virus DNA

5.1 Dr J. Esposito and Dr I. Damon gave respective presentations on "Sequence diversity, clues to the origin and virulence differences of variola virus" and "Inferring the phylogeny of variola virus from genomic single nucleotide polymorphisms (SNPs) analysis – future diagnostic applications". These presentations approached phylogenetic analysis of variola virus from different directions and were based on sequence information of whole genomes available for different strains. It was stated that:

- 40 complete variola virus genome sequences had now been determined and that a manuscript describing these had been prepared for publication;
- three main clades of virus show an evolutionary history from west African major strains to Alastrim minor to Asian major strains. The latter contained a subclade of non-west-African major and minor variants;
- areas of gene/sequence losses are located within the left and right end regions of the genome. Gene loss (negative selection) suggests that variola major preceded the variola minor viruses;
- SNPs could be used to map diversity and identify possible virulence factors. A number of candidate proteins, including immunomodulators and transcription factors might be involved in the major to minor virulence changes;
- SNPs could be used to establish a sequence matrix for the production of phylogenetics trees based on clustal analysis. These trees were not significantly different to those based on whole genome information;
- analysis of the SNP matrix indicates that variola major and Alastrim minor diverged from a common ancestor and evolved independently. West African variola virus strains from the collection have a common ancestry with the Brazilian Alastrim minor strains;
- SNP matrix analysis could be used in future diagnostic applications.

5.2 The Advisory Committee then considered what further essential research on diagnosis and sequence analysis required access to live variola virus. It was noted that the researchers involved had produced a considerable amount of information and that this could be used for diagnosis, detection, strain differentiation and forensic analysis. However, the Committee's view was that no further essential research that required access to live variola virus was needed in these areas. A view was expressed that access to live virus was still needed to provide material to produce standardized reagents for diagnostic and other tests, however, in the main, there would be no significant impact on public health if further work in this area was curtailed.

5.3 There were three provisos. First, the virus isolates in the United States and Russian repositories have very little overlap and so a case could be made to sequence more Russian strains. Second, further studies on the diversity of orthopoxviruses, and variola viruses in particular, could facilitate the development of animal models to show that these are faithful representations of

human smallpox. Last, it was not necessary or possible to provide validated, quality-controlled diagnostic capability for smallpox laboratories in all countries. WHO is willing to facilitate access to diagnostics when needed through the international laboratory networks.

5.4 Subject to assurances on these provisos, the Advisory Committee concluded that no further essential research that necessitated access to live stocks of variola virus was needed to provide additional information on diagnosis, detection and sequence analysis. In so doing, it recommended that scabs from monkeys infected with variola viruses should be retained to validate alternative diagnostic tests.

6. Update on animal models

6.1 Dr E. Ryabchikova described "Comparative studies of morphologic parameters of viral replication and inflammatory response in chick embryos infected with cowpox and smallpox viruses". She noted that:

- cowpox virus (strain EP-2) and variola virus (strain Ind-3a) produced different amounts of extracellular enveloped virus particles following growth in Vero and chick embryo cells;
- cowpox and variola viruses produced different inflammatory responses on chick chorioallantoic membranes (CAM) and these were investigated by electron microscopy;
- variola virus can induce apoptosis in leukocytes of the CAM whereas cowpox virus does not.

6.2 Dr P. Jahrling described progress in the development and refinement of the variola virus primate model noting that progress had been slow because of lack of access to the BSL-4 facilities during the past year. He stated that :

- intravenous infection of cynomolgous monkeys with high doses of Harper and India strains of variola virus provided the most promising model. The number of lesions produced and biochemical parameters could be related to the input dose;
- microarray technologies showed that there were temporally coordinated patterns of gene expression in peripheral blood, involving both up and down regulation, at different post-infection times;
- the current animal model created an instant viraemia, which eclipsed the normal incubation and prodromal phases in humans, and that this represented a significant disadvantage. However, it may be possible to refine the model by using different challenge routes (particularly aerosols with large particle sizes or droplets);
- the intention was to conduct a serial sacrifice study to fully characterize intermediate stage disease and disease progression parameters;
- the object of this work was to build bridges to the intravenous monkeypox model so that this would be acceptable to the United States Food and Drug Administration (FDA) to satisfy their licensing requirements for new antiviral

compounds and vaccines. Further work was needed to realize this objective but the Advisory Committee was confident that this could be achieved relatively quickly.

7. Review of antiviral candidate drugs

7.1 Dr J. Huggins introduced a series of presentations that reviewed the status of research on the search of antiviral agents against human pathogenic orthopoxviruses. He noted that:

- some 1700 (out of 2270) potential antiviral compounds from inventories held by the United States National Institute of Allergy and Infectious Diseases (NIAID), Prestwick, GlaxoSmithKline (GSK), Gilead Sciences and Stanford Research Institute (SRI), had been screened for relevant activity. Of these, 74 (4%) have demonstrable activity against vaccinia and cowpox viruses and so warrant further investigation using variola virus;
- useful lead compounds, including variola virus morphogenesis inhibitors, have been identified.

7.2 Dr J. Huggins then gave a paper entitled "An update on a search for antivirals against human-pathogenic orthopoxviruses". This was given on behalf of Dr E. Belanov and his colleagues who unfortunately could not attend this meeting. He indicated that:

- other compounds including 1,2,4-triazine and N1–oxyadenosine derivatives, with limited toxicity profiles and good antiviral activity against cowpox, vaccinia, monkeypox and ectromelia viruses, have also been identified. These may have different mechanisms of action to cidofovir.

7.3 Finally, Dr J. Huggins described "The evaluation of new chemical entities for orthopoxvirus infections using in vitro screening and animal model systems" during which he noted that:

- cidofovir remains the preferred drug candidate and initial results indicate that it can be used for both prophylaxis and post-exposure therapy;
- significant progress has been made towards gaining an FDA license for cidofovir based on the new Animal Efficacy Rule, which allows approval of an antiviral compound based on demonstration of efficacy in animal models where human clinical trials are not possible. Licensure according to this rule, originally developed for animal toxicity studies, requires application of good laboratory practices (GLP) standards and the United States Army Medical Research Institute for Infectious Diseases (USAMRIID) scientists have gone to considerable efforts to develop protocols and to upgrade laboratory equipment in order to comply with these standards. Discussions are under way with the FDA to allow documentation of efficacy, in both the monkeypox and variola virus lesional primate models, using reduced mortality, lesion counts, and viral load as indicators. The new rule might circumvent the need, for the purpose of licensing new antiviral drugs, of an animal model of smallpox that closely resembles clinical disease in humans.

- considerable work has been done on cidofovir administered orally, which is showing useful efficacy parameters and which can be used to provide supporting data for bridging between animal and human studies;
- cidofovir treatment was shown to decrease viral load and improve outcome measured by morbidity and mortality. There is an Investigational New Drug (IND) application advocating the use of cidofovir for the treatment of adverse reactions to vaccinia immunization that is refractile to treatment with vaccinia immune globulin (VIG);
- access to variola virus recombinants expressing green fluorescent protein would greatly facilitate and accelerate the drug screening programme.

7.4 Dr D. Kalman described his research on the involvement of host tyrosine kinases of the Abl and Src subfamilies in infections caused by pathogenic *E. coli* and orthopoxviruses. Tyrosine kinases have long been recognized to become dysregulated during oncogenic transformation. For example, dysregulation of Abl causes chronic myelogenous leukemia (CML). Importantly, relatively specific inhibitors have been developed and are currently used to treat such cancers in humans. One of these, Gleevec[®], is used to treat CML, and is relatively free of toxic side-effects even with protracted administration, and is commercially available.

7.5 Dr Kalman provided evidence that motility of vaccinia virus and release of infectious particles from cells, processes important for dissemination of poxvirus infections in vivo, depend on Src and Abl kinases. Accordingly, evidence was presented showing that Gleevec[®] reduced release of infectious particles in vitro, and reduced vaccinia viral load in infected mice by some 5 orders of magnitude.

7.6 Dr Kalman suggested that drugs such as Gleevec[®] may be useful in treating poxvirus infection or complications associated with vaccination, a possibility currently being tested. Thus, these results represent the development of a commercially available and relatively safe antiviral treatment strategy to complement cidofovir. Dr Kalman raised the possibility that the general strategy of using such inhibitors may be applicable to a broad range of human pathogens, and that because these drugs affect host and not pathogen, they are less likely to engender resistance compared with conventional drugs directed at microbial targets.

8. Proposed revisions of the 1994 recommendations of the Ad Hoc Committee on Orthopoxviruses

8.1 Dr R. Wittek gave the background to the proposed revisions of the 1994 recommendations of the Ad Hoc Committee on Orthopoxvirus Infections. He indicated that the Ad Hoc Committee had mandated the WHO Advisory Committee on Variola Virus Research to provide expert opinion and advice to WHO on issues that related to the distribution of variola virus DNA, the simultaneous handling of variola virus and other orthopoxviruses, in vitro synthesis of variola virus DNA and mutagenesis of orthopoxvirus DNA, the expression of individual variola virus genes in other orthopoxviruses and the generation of a variola virus expressing the green fluorescent marker protein. After extensive discussion the Advisory Committee provided the following advice and recommendations.

8.2 Distribution of variola virus DNA

- Fragments of variola virus DNA, not exceeding 500 base pairs in length, may be distributed between identified laboratories for use as positive controls or standards in diagnostic kits, providing collectively they do not exceed 20% of the total genome size. In accordance with the 1994 Ad Hoc Committee recommendations, larger fragments of variola virus DNA, collectively not exceeding 20% of the total genome size, may be obtained from either one of the two WHO Collaborating Centres holding variola virus, provided WHO has granted permission.
- Full-length genomic variola virus DNA may be exchanged between the two WHO Collaborating Centres holding variola virus subject to export/import approval from the regulatory authorities.
- DNA chips containing multiple, short variola virus DNA fragments up to 100 nucleotides in size, covalently bound to a solid support, may be produced and distributed for genome sequencing, even if the total amount of DNA on the chip represents more than 20% of the variola virus genome. If, for the production of chips, oligonucleotides are synthesized in solution rather than directly on a solid support, then both their synthesis and use cannot take place in laboratories where orthopoxviruses are handled.

8.3 Simultaneous handling of variola virus and other orthopoxviruses

- Variola virus can only be handled under BSL-4 conditions in the existing WHO Collaborating Centres holding variola virus. Other orthopoxviruses can be handled simultaneously in the same BSL-4 laboratory to facilitate drug screening providing this does not involve co-infection of cells and providing all infected materials are properly decontaminated and disposed of at the end of the experiment.

8.4 In vitro synthesis of variola virus DNA and mutagenesis of orthopoxvirus DNA

- Attempts to synthesize full-length variola virus genomes or infectious variola viruses from smaller DNA fragments are strictly forbidden.
- In vitro synthesis of variola virus DNA, or any DNA encoding a variola virus polypeptide, where the length of the DNA exceeds 500 base pairs requires approval from WHO. Similarly, mutagenesis of orthopoxvirus DNA of larger than 500 base pairs, with the aim of producing the corresponding variola virus DNA sequence again requires permission from WHO. Under no circumstances can laboratories, other than the WHO Collaborating Centres hosting the variola virus repositories, hold DNA comprising more than 20% of the total genome.

8.5 Expression of individual variola virus genes in other orthopoxviruses

- The Advisory Committee emphasized that this work should be done exclusively for public benefit, to obviate the use of live variola virus and facilitate antiviral drug and vaccine development. It recommended that the expression of natural or engineered variola virus genes in orthopoxvirus vectors might be permitted if:
 - the research protocols and risk assessments are reviewed for biosafety and recombinant DNA concerns and approved by appropriate institutional authorities and WHO in accordance with national regulations and WHO resolutions and recommendations;
 - those generating and handling such recombinant viruses should have their smallpox vaccination status approved by their national and institutional authorities;
 - not more than one variola virus gene is inserted into the virus vector. Any proposal to insert more than one variola virus gene into an orthopoxvirus must be considered by the WHO Advisory Committee on Variola Virus Research and approved by WHO;
 - the experiments are performed at BSL-3 or higher containment and consideration is given to the use of high-efficiency particulate air (HEPA) filtration of exhausted air as an additional biosafety requirement for these laboratories;
 - work with such recombinant viruses is done in a laboratory in which no other orthopoxvirus is present.

8.6 Generation of a variola virus expressing the green fluorescent marker protein

The Advisory Committee noted that this work was needed to accelerate the screening for antiviral compounds and that this would reduce the time that laboratory workers are handling live variola virus. In addition, it was noted that expression of the green fluorescent marker protein in other orthopoxviruses has not resulted in increased virus virulence.

The Advisory Committee recommended that the proposed work should proceed providing:

- a compelling justification for producing such viruses is provided to the Scientific Sub-Committee of the WHO Advisory Committee on Variola Virus Research. This committee will then recommend approval/disapproval of the project by WHO;
- a detailed risk analysis is performed to demonstrate that insertion of the marker gene is very unlikely to increase the virulence of the derivative variola virus;
- the research for which the derivative virus is produced is specified and limited and the viral reagent is destroyed once the immediate objectives have been achieved.

Annex 1. Agenda

4 November 2004

9:00–9:05 Welcome, Purpose of Meeting

9:05–9:15 Report of the Secretariat – D. Lavanchy

9:15–9:45 Update on variola virus strains in collection

- Update on the variola virus stocks in the Russian collection
– L. Sandakhchiev (VECTOR – Russian Federation)
- Update on the variola strains at the WHO Collaborating Centre
– I. Damon (Centers for Disease Control and Prevention – USA)

09:45–10:15 Update on diagnostic assays

- Review and update on reagents and diagnostics: nucleic acids, preparing for FDA review, and monoclonal characterization – I. Damon (Centers for Disease Control and Prevention – USA)
- Detection of orthopoxviruses and simultaneous identification of smallpox virus
– H. Meyer (Institute of Microbiology of the Bundeswehr – Germany)

10:15–10:45 Tea/coffee break

10:45–11:00 Update on diagnostic assays (continued)

- Oligonucleotide microarray in differentiation of orthopox and herpesviruses
– V. Mikhailovich (Engelhardt Institute of Molecular Biology – Russian Federation)

11:00–11:30 Update on antibodies

- Human combinatorial antibodies against orthopoxviruses
– N. Tikunova (VECTOR – Russian Federation)
- Cross-reactive neutralizing monoclonal antibodies to the orthopoxviruses
– V. Loktev (VECTOR – Russian Federation)

11:30–12:00 Update on vaccines

- Creation of the candidate live polyvalent vaccine against human immunodeficiency virus, hepatitis B virus, and orthopoxviruses
– S. Shchelkunov (VECTOR – Russian Federation)
- The study of reactogenicity, safety and immunogenicity of recombinant variola and hepatitis B bivalent vaccine for oral administration in humans
– A. Sergeev (VECTOR – Russian Federation)

4 November 2004 (continued)

- 12:00–12:30 Sequence analysis of variola virus DNA
- Sequence diversity clues to the origin and virulence differences of variola virus – J. Esposito (Centers for Disease Control and Prevention – USA)
- 12:30–13:45 Lunch
- 13:45–14:15 Sequence analysis of variola virus DNA (continued)
- Inferring the phylogeny of variola virus from genomic SNPs analysis – future diagnostic applications? – I. Damon (Centers for Disease Control and Prevention – USA)
- 14:15–15:15 Update on animal models
- Comparative studies of morphologic parameters of viral replication and inflammatory response in chick embryos infected with cowpox and smallpox viruses – E. Ryabchikova (VECTOR – Russian Federation)
 - Title to be announced – P. Jahrling (United States Army Medical Research Institute for Infectious Diseases – USA)
- 15:15–15:45 Tea/coffee break
- 15:45–16:00 Review of antiviral candidate drugs
- Status of research on the treatment of smallpox-like disease in variola and monkeypox primate models with intravenous cidofovir – J. Huggins (United States Army Medical Research Institute for Infectious Diseases – USA)
- 16:00–16:30 Discussion

5 November 2004

- 09:00–10:30 Review of antiviral candidate drugs (continued)
- UK research on medical countermeasures to smallpox
– D. Ulaeto (Defence Science and Technology Laboratory – England)
 - Update on search for antivirals against human-pathogenic orthopoxviruses – E. Belanov (VECTOR – Russian Federation)
 - Evaluation of new chemical entities for orthopoxvirus infections using in vitro screening and animal model systems – J. Huggins (United States Army Medical Research Institute for Infectious Diseases – USA)
 - Disabling orthopoxviruses: from cell biology to a translational strategy
– D. Kalman (Emory University – USA)
- 10:30–11:00 Tea/coffee break
- 11:00–12:00 Proposed revisions of the 1994 recommendations of the Ad hoc Committee on Orthopoxvirus Infections
- Introduction – R. Wittek
 - Discussion
- 12:00–13:30 Lunch
- 13:30–15:00 General discussion and preparation of draft recommendations
- 15:00–15:30 Tea/coffee break
- 15:30–17:00 Consensus on recommendations

Annex 2. List of participants

Advisory Committee

Dr Isao Arita, Chairman, Agency for Cooperation in International Health, Kumamoto City, Kumamoto, Japan

Dr Robert Drillien, Institut de Génétique et de Biologie Moléculaire et Cellulaire, Illkirch, Cedex, France

Dr Mariano Esteban, Director, Centro Nacional de Biotecnología, Campus Universidad Autónoma, Cantoblanco, Madrid, Spain

Dr David H. Evans, Professor and Chair, Medical Microbiology and Immunology, University of Alberta Edmonton, Alberta, Canada

Dr James Hughes, Director, National Center for Infectious Diseases, Centers for Disease Control and Prevention, Atlanta, USA

Dr Shashi Khare, Microbiology Department, National Institute of Communicable Diseases, New Delhi, India

Professor Georg Pauli, Zentrum für Biologische Sicherheit (ZBS) Hochpathogene virale Erreger (ZBS 1) Berlin, Germany

Dr André D. Plantinga, Netherlands Vaccine Institute, Bilthoven, Netherlands

Dr Tony Robinson, Senior Principle Research Scientist, CSIRO Sustainable Ecosystems, Canberra, Australia

Dr Li Ruan, Laboratory Chief, Institute for Viral Disease Control and Prevention, Chinese Center for Disease Control and Prevention, Beijing, China

Professor Lev S. Sandakhchiev, Director General, State Research Center of Virology and Biotechnology, VECTOR, Novosibirsk Region, Russian Federation

Dr Hermann Schatzmayr, Head, Virology Department, Instituto Oswaldo Cruz, Rio de Janeiro, Brazil

Professor Geoffrey L. Smith, Wellcome Trust Principal Research Fellow, Department of Virology, Faculty of Medicine, Imperial College London, London, England

Dr Robert Snoeck, Senior Researcher, Katholieke Universiteit Leuven, Rega Institute, Minderbroedersstraat, Leuven, Belgium

Professor Robert Swanepoel, Special Pathogens Unit, National Institute for Virology, Sandringham, South Africa

Professor Muyembe Tamfum, Director, Institut National de Recherche Bio-Médicale (INRB), Kinshasa, Democratic Republic of the Congo

Professor Dr Prasert Thongcharoen, Division of Virology, Department of Microbiology, Faculty of Medicine Siriraj Hospital, Bangkok, Thailand

Dr Henda Triki, Chief, Laboratory of Clinical Virology, Institut Pasteur de Tunis, Tunis, Tunisia

Advisers to the Committee

Dr Antonio Alcami, Centro Nacional de Biotecnología, CSIC Campus Universidad Autónoma, Madrid, Spain

Dr Inger K. Damon, Poxvirus Section, Viral Exanthems and Herpesvirus Branch/DVRD/NCID, Centers for Disease Control and Prevention, Atlanta, USA

Dr Joseph J. Esposito, Coordinator of Collaborative Research, Centers for Disease Control and Prevention, Atlanta, USA

Dr Daniel Garin, Head of Virology Lab, Centre de Recherche du Service de Santé des Armées (CRSSA), Grenoble, France

Dr Donald A. Henderson (unable to attend), Director Johns Hopkins Center for Civilian Biodefense Studies, School of Hygiene and Public Health, Baltimore, Maryland, USA

Dr John W. Huggins, Chief, Department of Viral Therapeutics, Virology Division, United States Army Medical Research Institute of Infectious Diseases (USAMRIID), Maryland, USA

Dr Lauren Iacono-Connors (unable to attend), Senior Advisor to the Center Director, Center for Biologics Evaluation and Research (CBER), Food and Drug Administration, Maryland, USA

Dr Peter B. Jahrling, Principal Scientific Advisor, United States Army Medical Research Institute of Infectious Diseases (USAMRIID), Maryland, USA

Dr Ichiro Kurane, Director, Department of Virology, National Institute of Infectious Diseases, Tokyo, Japan

Dr Brian Mahy, Scientific Research Advisor, National Center for Infectious Diseases, Centers for Disease Control and Prevention, Atlanta, USA

Dr Michael Merchlinsky, Senior Investigator, Food and Drug Administration (FDA), Office of Vaccines Research and Review, Division of Viral Products/Laboratory of DNA Viruses, Maryland, USA

Dr Bernard Moss, NIAID, National Institute of Health, Maryland, USA

Dr Elena I. Ryabchikova, Head, Laboratory of Ultrastructure Studies and Pathomorphology, State Research Center of Virology and Biotechnology VECTOR, Novosibirsk region, Russian Federation

Professor Alexandr N. Sergeev, Head, Department of Experimental Aerobiology Research, State Research Center of Virology and Biotechnology VECTOR, Novosibirsk region, Russian Federation

Professor Sergei N. Shchelkunov, Head, Department of Molecular Biology of Genomes, State Research Center of Virology and Biotechnology, VECTOR, Novosibirsk Region, Russian Federation

Dr Nina V. Tikunova, Head, Laboratory of Recombinant Proteins, State Research Center of Virology and Biotechnology VECTOR, Novosibirsk region, Russian Federation

Dr David Ulaeto, Scientific Leader, Defence Science and Technology Laboratory, Ministry of Defence Porton Down, Wiltshire, England

Observers

Dr Evgueny F. Belanov (unable to attend), Head, General Virology Laboratory, State Research Center of Virology and Biotechnology VECTOR, Novosibirsk region, Russian Federation

Dr Peter D. E. Biggins, Head of IRS, DERA-CBD, CB Systems, Porton Down, Wiltshire, England

Dr Mike Bray, Biodefense Clinical Research Branch, Office of Clinical Research, NIAID, National Institutes of Health, Maryland, USA

Mr Marc Jasper, Program Manager, Cooperative Biological Research Project, Center for Nonproliferation Studies, Monterey Institute of International Studies, Washington, USA

Dr Daniel Kalman, Department of Pathology and Laboratory Medicine Emory University, Atlanta, USA

Dr James W. LeDuc, Director, Division of Viral and Rickettsial Diseases, National Center for Infectious Diseases, Centers for Disease Control and Prevention, Atlanta, USA

Professor Valery B. Loktev, Head, Department of Molecular Virology, State Research Center of Virology and Biotechnology VECTOR, Novosibirsk region, Russian Federation

Dr Hermann Meyer, Institute of Microbiology, Munich, Germany

WHO Secretariat

Dr A. Asamoah-Baah, ADG/CDS

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