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WHO Advisory Committee on Variola Virus Research

Report of the Eighth Meeting

Geneva, Switzerland
16 –17 November 2006

EPIDEMIC AND PANDEMIC
ALERT AND RESPONSE

World Health Organization

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Contents

1. Introduction

1.1 Dr Cathy Roth welcomed participants to the eighth meeting of the Advisory Committee on Variola Virus Research on behalf of Dr Mike Ryan. She indicated that the World Health Assembly (WHA) is showing an increased interest in research involving live variola virus and that it needs clear arguments to support continuation of such research and that it will be important to identify the public health benefits of this research. She also reminded the meeting that participants are sub-divided into three groups – full members, who would be responsible for decision-making, advisers, who would be able to participate fully in the discussions and so contribute to the development of the Advisory Committee's recommendations, and observers.

1.2 Dr Cathy Roth ended her introductory remarks by reminding the meeting that Professor Lev Sandakhchiev had suddenly died in the past year and she asked the participants to spend a few moments in silent recollection.

1.3 The Advisory Committee elected Professor Geoffrey Smith as Chairman and Dr Robert Drillien as Rapporteur. Participants then introduced themselves.

2. Report from the Secretariat

2.1 Dr Daniel Lavanchy reminded participants that the Advisory Committee had been convened for the first time in 1999 with the purpose of identifying areas of essential research that depended on access to live variola virus. Since then, the Committee has met annually to review the progress of approved research. The meeting report would be submitted to the WHO Director-General and then to the Executive Board and finally the WHA. The report should remain confidential until the final version was posted on the WHO web site.

2.2 Dr Lavanchy then stated that there had been dissent in the past over proposals to destroy the samples of live variola virus held by the two WHO Collaborating Centres in the USA and Russia. This had created pressures to define what R&D is essential and requires access to the live virus, and how long this research should continue. A resolution concerning the destruction of the variola virus samples was considered by the Executive Board, which had set up an Intergovernmental Working Group (IGWG) to discuss the issues. This Group subsequently met in April but failed to reach consensus agreement. This issue was discussed in a continuation of the IGWG working group during the WHA, which also failed to agree on a text. The WHA then decided that the resolution would be submitted for further consideration by the Executive Board in January 2007. The outcomes of this current meeting of the Advisory Committee need to be seen in this context, which clearly has ramifications in terms of funding for designated essential research, public health gains and benefit to individuals. The Secretariat indicated that the Advisory Committee should focus on an assessment of progress on the approved research programmes and that issues associated with destruction of live virus strains were not pertinent to the current committee meeting. It

would be important for the meeting report to capture accurately the views of all members of the Advisory Committee.

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

3.1 The WHO Collaborating Centre for Smallpox and other Poxvirus Infections in Atlanta, USA continues to maintain one of two consolidated, international collections of variola virus strains. The majority of these viruses were isolated originally on embryonated eggs and collected during the final years of the eradication programme. The virus collection is maintained in two separated freezers, one of which is a back-up freezer that has remained largely untouched.

3.2 The inventory is checked annually. Access to the repository is limited, and coordinated through the use of a standard operating protocol, which requires the presence of at least two persons: one from the scientific programme and one from biosafety or biosecurity. Access to the repository is thus strictly controlled and usually involves at least three personnel, one of which is from the security department. Secure databases, which address WHO recommendations as well as US Select Agent requirements, have been developed to track usage of variola virus and this information is provided to WHO on an annual basis.

3.3 Dr Damon reminded the Advisory Committee that the repository contained 451 samples, isolates or strains. Forty-five viable isolates had been subjected to a full nucleotide sequence analysis, the results of which had been published in *Science* in 2006. A single nucleotide polymorphism (SNP) analysis has demonstrated that there are two main phylogenetic groups. The larger, which could possibly be subdivided into two, contained the Asian and African isolates. The smaller contained the Alastrim and West African strains.

3.4 Dr Damon indicated that work on trying to establish biological properties of the isolated viruses was ongoing. She indicated that the study had demonstrated already that there was no correlation between the formation of comet-shaped plaques (indicative of release of extracellular enveloped (EEV) virus) and virulence (as reflected by case-fatality rates). It was noted that studies to investigate the roles of intracellular virus versus EEV in transmission between hosts could be performed using other orthopoxviruses as surrogates.

3.5 Professor Drozdov then updated the Advisory Committee on the status of the variola virus repository held in the Russian collection at the WHO Collaborating Centre for Orthopoxvirus Diagnosis and Repository for Variola Virus Strains and DNA, State Research Center of Virology and Biotechnology "VECTOR". The collection is comprised of 120 strains, including 17 clinical isolates, held in a total of 891 ampoules and tubes. No work involving live virus material had been done during the current reporting year due to delays in gaining WHO approvals for proposed research projects and to the need to upgrade the existing laboratory infrastructure.

3.6 At present, all live virus stocks are held in a secured store in Building 1 where access is restricted by defined directives and regulations to two designated personnel at any one

time when accompanied by an armed guard. The -70°C storage freezers are monitored continuously and have appropriate alarms with backup facilities being available. Upgrading of the current infrastructure is in progress with the intention of eventually establishing a permanent repository in Building 6 (the current BSL-4 facility for variola virus work).

3.7 Professor Sergei Shchelkunov then described how preparations of variola virus DNA were being conserved in three ways – as full length genomic DNA preparations, as extended PCR amplicons covering the full genome and as cloned DNA in hybrid plasmids. Genomic DNA was now available from 29 strains, DNA amplicon collections were available from some 17 strains and there were 13 collections of cloned DNA fragments. Documentation was available for all materials, describing their derivation, method of preparation, storage, etc. and a catalogue is available through the WHO annual report.

3.8 In response to questions, it was confirmed that telomeres had not been cloned or sequenced and that infectious virus and DNA can be isolated from some, but not all, scab materials. The Russian scientists considered the most reliable method for long term conservation of variola virus DNA to be the cloning as hybrid plasmids.

4. Need for further sequencing of variola virus DNA

4.1 This was recognized as a contentious issue because the Advisory Committee had recommended previously that no further full-length genomic DNA sequences were needed. The Committee was reminded that the complete DNA sequence of 45 variola virus strains from the CDC repository had been published and that there was now a good understanding of genetic diversity involved. It was accepted that there were two main phylogenetic groups (clades) and that most viruses would fall within this grouping. There were some outstanding questions regarding the diversity of strains in the two collections, particularly with respect to India 67, Nepal 73 and Rwanda 70. It was also recognized that there was incomplete coverage in terms of geographical origin and virulence of virus strains.

4.2 In response to a question regarding the need for further work in this area, it was stated that a balance was needed between sequences that might be scientifically interesting and those that were essential for public health purposes. There might be scientific benefit in having access to more full-length genomic DNA sequence information from which further phylogenetic relationships could be determined, but it was questioned how relevant this might be in terms of protecting public health.

4.3 The Committee discussed whether or not additional full-length nucleotide sequence information would be valuable and if this could be obtained from DNA preparations which were already available. Such sequence information could be useful for determining evolutionary relationships between viruses and for diagnostic/forensic purposes. Within the Russian scientific community, it was felt there was sufficient DNA already available to fulfill these needs and therefore, that no live viruses needed to be grown to provide additional material to generate more sequence information. This issue may need to be reconsidered pending review of literature on known variola

viruses. In addition, it was evident that the genomes of another 29 variola viruses in the Russian collection could be sequenced without any further need for work with live virus.

5. Update on diagnostics and vaccines

5.1 The WHO Collaborating Centre at CDC provided preliminary results on the development of a solid membrane supported assay suitable for field use, which could be used to evaluate sera for the presence of orthopoxvirus (or varicella virus) reactivity in an individual presenting with rash illness. Additional studies will be needed to evaluate the assay robustness, stability, sensitivity and specificity.
Studies on two monoclonal antibodies (mAb) targeting variola virus were described. The mAb may be valuable as a component of a variola-specific antigen capture assay.

5.2 Professor Geoffrey Smith reminded the Committee of the need for a safer smallpox vaccine and an increased understanding of the immune response to smallpox vaccine in order to evaluate new candidate vaccines and to have a benchmark against which residual immunity could be compared. Professor Smith's group has studied the specificity of the antibody response in a cohort of UK health-care workers who were vaccinated in 2003 with the vaccinia virus strain Lister. They demonstrated that protein B5 of the extracellular enveloped virus is the only target of antibodies capable to neutralize this virus form, even though other viral envelope proteins may play a role in inducing other types of immune responses.

5.3 On the other hand, several viral proteins (including D8, A27 and H3) on the surface of the intracellular virus are targeted for neutralization by antibodies. Analysis of the antigen-specific immune response either over a one-year period or over a number of years showed, in agreement with other reports, a long lasting antigen-specific immune response. Finally, a comparison of two classical vaccines to one attenuated vaccine indicated that the latter was deficient in inducing a high level as well as a full range of antigen-specific antibodies. These data provide one set of standards for evaluating new smallpox vaccines.

5.4 Dr Inger Damon reported ongoing work to evaluate smallpox vaccines by using variola virus as a neutralizing target. Preliminary findings indicated there might be some differences in the ability of human immune sera to neutralize variola virus and vaccinia virus. Comparison of neutralizing antibodies induced against variola virus or vaccinia virus in volunteers vaccinated with Dryvax or MVA using distinct protocols in a larger population is under way.

6. Animal models

6.1 Dr Peter Jahrling updated the Advisory Committee on the current status of the non-human primate model of smallpox. One model comprised the intravenous inoculation of large amounts of variola virus, which invariably resulted in death of infected animals. The other model, more closely resembling classical human smallpox resulted

from the intravenous inoculation of smaller amounts of virus. He also described results obtained following an intratracheal route of exposure, which was considered superior to an aerosol route due to ease of administration of the virus, which resulted in more reproducible results and consequently required smaller numbers of animals.

6.2 The results of a sequential sacrifice study were described in which two groups of monkeys received doses of variola virus calibrated to cause either 30% mortality (similar to ordinary smallpox in humans) or 100% mortality (similar to haemorrhagic smallpox). These studies were designed to characterize better the progression of disease pathophysiology, in compliance with the FDA Animal Efficacy Rule. The results demonstrated that the expression of 244 genes (197 unique ones) was up-regulated in a dose-dependent way to infection whereas 177 genes (107 unique genes) had an inverse response to the infectious dose.

6.3 The conclusion was that a low dose intravenous variola virus infection of monkeys provided a valid pathophysiological disease model for human infections.

6.4 For both the lesional (low dose, ordinary smallpox) and haemorrhagic (high dose) models, disease progression, as demonstrated by gross and histological examination, did not appear until several days after significant virus replication had occurred. Sepsis was considered an important parameter in this process and the effect of recombinant activated protein C on this clinical manifestation was described. Considerable therapeutic benefit was obtained and it was agreed that further work to define the clinical efficacy of this compound was required.

7. Candidate antiviral drugs

7.1 Dr Dennis Hruby reviewed data available on the discovery and development of ST-246, a new candidate antiviral drug. The drug is 8000 times more potent than Cidofovir, can be delivered orally and is relatively easy to synthesize. It is effective against all tested orthopoxviruses, preventing the wrapping of intracellular mature virus (IMV) by intracellular membranes and thereby the formation of extracellular virus particles. The target of the drug is F13 (according to the nomenclature used for the vaccinia Copenhagen strain), a protein essential for the production of extracellular enveloped virus.

7.2 ST-246 is highly effective when given 4–72 hours post infection with a range of orthopoxviruses in small rodents. It can be used prophylactically and therapeutically and can even be given simultaneous with vaccination, without interfering with the immune response to the vaccine.

7.3 Studies for gaining regulatory approval of the drug are now in progress. The drug has a long biological half life of approximately 18 hours which suggests that a once-a-day oral regimen might be sufficient. Current information suggests that its bioavailability is good and that there are no adverse side effects. In vitro tests show that the antiviral effects of ST-246 are reproducible across different variola virus strains. Drug resistance to ST-246 can occur with an estimated frequency of 2.5×10^{-6}. ST-246 is considered

superior to Cidofovir preparations, which are in a more advanced state of drug approval.

7.4 Initial studies indicate that ST-246 is inherently stable and so strategies for creating stockpiles can be developed.

7.5 Dr John Huggins then gave an overview of the current status of antiviral drug development using the current monkeypox and non-human primate variola virus disease models. ST-246 was clearly seen as the drug of choice but Cidofovir could be used as the test case for licensure issues, particularly because its safety in humans did not need to be established. Cidofovir had a proven efficacy with respect to orthopoxvirus infections and protocols had been submitted to the US FDA for consideration under the Special Protocol Assessment Provision. If successful, this will enable the drug manufacturer (Gilead Sciences) to submit a proposal for regulatory approval for this indication. This will be done in parallel with further work on ST-246.

7.6 It was noted that ST-246 was a non-toxic inhibitor of variola virus spread that can be given orally. Clinical safety will be determined in humans and efficacy studies will be performed in non-human primate models of variola virus and monkeypox virus to support an application for orphan drug status of the compound. However, oral drugs may not be well tolerated in severely ill individuals and hence alternative formulations of ST-246 may need to be developed, which can be administered via different routes. The fact that ST-246 was highly specific in inhibiting the spread of orthopoxviruses was emphasized, as was that this could result in its wider deployment as a potent antiviral compound. Overall, ST-246 looked like an excellent drug candidate that has provided solid protection against challenge by different orthopoxviruses, including variola virus, in all models examined.

8. Virus neutralizing scFv antibodies against human pathogenic orthopoxviruses

8.1 Dr Tikunova described work to produce single chain antibodies (scFv) against orthopoxviruses by biopanning of phage display libraries constructed using cDNAs derived from vaccinia virus immunized volunteers. A number of scFv candidates were isolated and all of those that neutralized IMV (intracellular mature virus) were found to recognize a 35 kDa protein encoded by the J3L ORF (open reading frame) of cowpox virus. The antibodies were also shown to display a very high affinity for their target antigen and were thus considered as promising candidates for neutralization of orthopoxviruses, including variola virus. Dr Moss mentioned the isolation of a panel of very high affinity scFv antibodies derived from chimpanzee bone marrow at the National Institutes of Health, USA (NIH).

9. Distribution of variola virus DNA fragments and transfer of such material to third parties

9.1 Distribution of variola virus DNA fragments has been authorized in the past for specific human health related research according to rules set out by the WHO and according to

recommendations made by the *Ad Hoc* Committee on Orthopoxvirus Infections in 1994, and more recently by the present Committee. An overview of the laboratories that had obtained limited regions of variola virus DNA with WHO approval was presented.

9.2 The CDC has so far been the only source of such material. The transfer of such material has been conditional on the presentation of annual reports describing its use to WHO. The Committee recognized that reporting has been incomplete and advised the WHO Secretariat to request reports from laboratories, and, in the event that the DNA samples were no longer being used for the work planned, that they be destroyed.

9.3 The Committee was requested to state its opinion on the acceptability of transfer of variola virus DNA samples from laboratories authorized to work with this material to third parties. It was recommended that such transfer could occur only after approval had been obtained from WHO and with a material transfer agreement from the WHO Collaborating Centre.

9.4 The Committee also debated whether the current WHO guidelines for distribution of variola virus DNA samples were appropriate in light of recent requests related to the development of subunit vaccines, the regular technical advances as well as careful risk assessment. This discussion was triggered in part by recent developments in synthesizing genes and concerns that WHO restrictions on distribution and manipulation of variola virus genes may not be widely recognized by the scientific community. It was agreed that it would be useful to set up a technical subcommittee to review the rules and propose revisions if deemed necessary and report back to the next Committee meeting. In order to ensure general awareness of the regulations governing the distribution of variola virus DNA, the Committee recommended that an updated set of rules be widely distributed to country representatives and regulatory bodies, and posted on the WHO web site.

10. Outbreak of a cowpox-like virus in zoo animals in Germany

10.1 Dr Pauli described a recent outbreak of a lethal orthopoxvirus infection in marmosets in a private German zoo. A series of tests enabled the identification of the infectious agent as a virus closely related to cowpox virus with distinct biological properties. The virus has been tentatively designated as Calpox virus and was most likely transmitted to the monkeys by wild mice. The incident raises concern that a similar transmission may occur into the human population, but it also provides a highly sensitive virus/host system to study anti-orthopoxvirus drugs and vaccines. Dr Schatzmayr reminded the Committee that in recent years as many as 7 pathogenic vaccinia virus strains have been isolated from infected cattle, as well as man, in Brazil.

11. Operational considerations for smallpox diagnosis

11.1 Dr Inger Damon described some of the considerations for maintaining an adequate capacity to undertake a definitive diagnosis for smallpox. She described both clinical

and laboratory algorithms for this purpose. The focus was on the differential diagnosis of febrile vesicular rash illness. The issues relevant to smallpox diagnosis that were discussed included biosafety and biosecurity, transportation of diagnostic specimens, QA/QC, the maintenance of trained personnel and communication of results. Further discussions are warranted about what the capacities of other countries are in terms of supporting containment laboratories, what safety levels are needed for smallpox diagnostics, and about what is sufficient under defined circumstances.

11.2 During discussion it was stated that sequences of PCR primers and targets needed for PCR-based smallpox diagnosis had been published and so were generally available. In addition, a PCR kit was available commercially. It was also noted that real time diagnostic PCR hardware was also available for field use.

11.3 The Advisory Committee recommended that WHO should establish an informal virtual laboratory network dedicated to the diagnosis of orthopoxviruses. This would provide an infrastructure whereby those engaged in diagnosis could exchange views, information on current diagnostic procedures and reagents. It was noted that there could not be a single diagnostic strategy as much would depend on the national infrastructure and capability. It would be important to put in place a mechanism by which information relevant to the diagnosis of smallpox could be disseminated and materials for confirmation of diagnosis transported.

12. New/updated proposals submitted to WHO

12.1 In prior meetings the Committee recommended that all research carried out with live variola virus in the two Collaborating Centres be essential for public health benefit and time-limited. In light of this, it had been decided at the last meeting of the Committee that the two laboratories involved in such studies renew proposals for any work they were conducting and submit proposals for any work planned.

12.2 A scientific subcommittee was set up to review the new research proposals. Dr Riccardo Wittek summarized the work of the subcommittee and the decisions taken by WHO after receiving the reviews. He indicated that 7 projects had been approved (a list of approved projects is appended to this report as Annex.1). Decisions on 7 projects were still pending and 5 projects had been rejected. He noted that those rejected did not meet the criteria for essential research that required access to live variola virus.

12.3 Suggestions were also made by Committee members to improve the process of reviewing research proposals on live variola virus. It was agreed that the decisions reached by WHO on research proposals should be sent to their authors within 2 months of the original submission. In the event of a rejection, anonymous reviews would be provided to the submitting investigators. Modified proposals could be resubmitted to WHO, and again reviewed within a 2-month period. Should the new submission be rejected unanimously by the subcommittee, then it would be recommended that such research should not be carried out. If rejected by a majority decision, the originators could request that the proposals be examined by the entire Committee, and its recommendation submitted to WHO.

12.4 Finally, it was agreed that the membership of the scientific subcommittee should be reviewed and that up to one-third of its membership should be rotated annually. Because of possible conflicts of interest, it was decided that the policy of excluding participation from staff of the Collaborating Centres should continue.

13. Miscellaneous

13.1 Dr Bernard Moss requested that the Advisory Committee reconsider the issue of introducing individual variola virus genes into other orthopoxviruses. The Advisory Committee had recommended in 2004 that this could be permitted providing:

- The research protocols and risk assessments are reviewed for biosafety and recombinant DNA concerns and approved by appropriate institutional authorities and the WHO Advisory Committee on Variola Virus Research 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.

- The experiments are performed at BSL-3 or higher containment and consideration is given to the use of 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.

13.2 The WHO Director-General had raised concerns about this recommendation because of the biosafety and biosecurity issues involved and asked the Committee to reconsider its recommendations. On reconsidering the recommendation in 2005 the Committee had therefore decided to withdraw the recommendation in its entirety.

13.3 Dr Moss argued that the scientific reasons for undertaking these experiments were still sound and that by constructing these recombinant viruses the development of vaccines and antiviral drugs would be accelerated. Some members of the Advisory Committee supported this view, particularly because the biosafety issues could be addressed on a case by case basis. Others remained concerned. The Chairman then asked the members of the Committee to vote on this recommendation. 6 members were for the proposal and 10 members were against it. The Advisory Committee therefore rejected the proposal.

13.4 Dr Previsani informed the Advisory Committee that the BSL-4 laboratories within the Collaborating Centres are inspected on a routine basis but that standardized protocols

for these inspections did not exist. Therefore she described the development of a tool that will be used to standardize these inspections between laboratories and from one visit to the next. This tool is being developed in consultation with the Collaborating Centres and other relevant biosafety and biosecurity groups. The Advisory Committee endorsed this concept but advised that the protocol should accommodate the fact that biosafety operations are addressed differently by different organizations. Dr Previsani indicated that she would keep the Advisory Committee informed of progress in development and implementation of this protocol.

13.5 The Secretariat updated the Committee on the status of the WHO smallpox vaccine stockpile, which currently contained 2.5×10^6 doses (mainly strain Lister) and is tested regularly for potency. Smaller quantities of a second generation vaccine are available but there are regulatory problems associated with its receipt. Some 31×10^6 doses had been pledged by Member States as part of the proposed stockpile pledged to WHO by Member States for use in an emergency. This was still significantly short of the 195×10^6 doses that hade been proposed.

13.6 The Secretariat indicated that the operational framework for release and mobilization of the vaccine stockpile was being developed further in the context of the new International Health Regulations. It was agreed that the Advisory Committee would be regularly briefed on the status of these stocks at its annual meetings.

13.7 Some Members States indicated that they were experiencing difficulties in obtaining small quantities of smallpox vaccine to vaccinate their frontline responders. The Secretariat indicated that WHO would not be able to supply vaccine from the global reserve for this purpose but agreed to assist Member States in identifying a source of vaccine. In response to a specific question, the Secretariat indicated that the current policy on smallpox vaccination was available on the WHO web site.

Annex 1. Approved research projects

- *The studies of the Russian national collection of the variola virus strains*
  a) Archiving of viable isolates in 2 secure locations;
  b) Selection and characterization of an Asian reference strain.

  Decision:
  Authorized, to be completed in 1 year.

- *Development of therapeutic variola antibodies*

  Decision:
  Authorized for 1 year, then re-evaluate.

- *Antiviral therapy of smallpox and other pathogenic orthopoxvirus infections resulting from terrorist or biological warfare release*

  Decision:
  Authorized for 2 years (until 31. 12. 07), then re-evaluate.

- *Refinement of the primate model for human smallpox to facilitate licensure of antiviral drugs and other countermeasures*

  Decision:
  Authorized for 2 years (until 31. 12. 07), then re-evaluate.

- *Protein-based diagnostic development*
  a) Development of variola virus-specific peptide-based assays for antigen detection and serological diagnosis.
  b) Testing of non-human primate sera against intact virus to ensure authenticity of recognition of synthetic peptides.
  c) Characterization of existing monoclonal antibodies using live variola virus.

  Decision:
  a) Does not require permission from WHO.
  b) Authorized until the end of 2007.
  c) Authorized until the end of 2007.

- *The use of live variola virus to evaluate therapeutic modalities: in vitro studies for the testing of antiviral candidate drugs*

  Decision:
  Authorized but progress to be reviewed annually.

- *The use of live variola virus to support less reactogenic vaccine development: Determine capacity of animal or human sera to neutralize variola virus IMV and EEV particles*

  Decision:
  Authorized until March 2007.

Annex 2. Agenda

16 November 2006

09:00 - 09:15 Opening - Purpose of Meeting - M. Ryan

09:15 - 09:30 Report of the secretariat – D. Lavanchy

09:30 - 09:45 Update on variola virus strains held in the US repository - I. Damon

09:45 - 10:00 Update on variola virus strains held in the Russian repository - S. Shchelkunov

10:00 - 10:15 Discussion on needs for further sequencing of variola virus DNA - all

10:15 - 10:30 Protein diagnostics - I. Damon

10:30 - 11:00 **Tea/Coffee Break**

11:00 - 11:15 Update on vaccines - G. Smith

11:15 - 11:30 Vaccine evaluation using a variola virus as a neutralizing target - I. Damon

11:30 - 12:00 Distribution of variola virus DNA fragments of up to 500 bp for other purposes than diagnostics (e.g. vaccines) - all

12:00 - 13:00 **Lunch**

13:00 - 13:30 Update on animal models - P. Jahrling (NIH/NIAID - USA)

13:30 - 14:00 ST-246: update - D. Hruby (Oregon State University - USA)

14:00 - 14:30 Review of antiviral candidate drugs - J. Huggins (USAMRIID - USA)

14:30 - 15:00 In vitro antiviral testing of ST-246 - I. Damon

15:00 - 15:45 **Tea/coffee break**

15:45 - 16:00 Producing virus-neutralizing scFv-antibodies against human-pathogenic Orthopoxviruses - N. Tikunova

16:00 - 16:30 Discussion about 3rd party transfer of DNA fragments larger than 500 bp - all

16:30 - 16:45 Consequences of an outbreak in zoo animals in Germany - G. Pauli

16:45 - 17:30 Mechanisms and operational aspects for the establishment of regional surge diagnostic capacity - I. Damon

17:30 - 19:00 Social event at the WHO main cafeteria

DAY 1 CLOSES

17 November 2006

09:00 - 09:15 New/updated research proposals submitted to WHO - R. Wittek

09:15 - 10:30 Miscellaneous

10:30 - 10:45 General discussion and preparation of draft recommendations

10:45 - 11:15 **Tea/coffee break**

11:15 - 12:30 General discussion and preparation of draft recommendations (continued)

12:30 - 13:30 **Lunch**

13:30 – 15:00 Consensus on recommendations

MEETING CLOSES

Annex 3. List of participants

Advisory Committee

Dr Aristide Aplogan,[1] Directeur des Programmes AMP Afrique, Agence de Médecine Préventive, Cotonou, Benin

Dr Isao Arita,[1] Chairman, Agency for Cooperation in International Health, Kumamoto City, Kumamoto, Japan

Dr Robert Drillien, Directeur de Recherche à l'INSERM, Institut de Génétique et de Biologie Moléculaire et Cellulaire, Illkirch, Cedex, France

Professor Ilya G. Drozdov, Director General, State Research Center of Virology and Biotechnology VECTOR, Novosibirsk Region, Russian Federation

Professor Mariano Esteban,[1] Head of Poxvirus and Vaccines, Centro Nacional de Biotecnologia, Campus Universidad Autonoma, Cantoblanco, Madrid, Spain

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

Dr Andrew Kiyu, Deputy Director of Public Health, Sarawak Health Department, Sarawak, Malaysia

Professor J. Michael Lane,[1] MD, MPH, Professor, Emeritus of Preventive Medicine, Emory University, School of Medicine, 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

Dr Akhilesh Chandra Mishra, Director, National Institute of Virology, Pune, India

Dr Jean-Vivien Mombouli, Directeur de la Recherche et de la Production, Laboratoire National de Santé Publique, Brazzaville, Congo

Professor Jean-Jacques Muyembe Tamfum,[1] Director, Institut National de Recherche Bio-Médicale (INRB), Kinshasa, Democratic Republic of Congo

Professor Peter Martin Ndumbe, Dean, Centre for the Study and Control of Communicable Diseases (CSCCD), Faculty of Medecine, Yaoundé, Cameroon

Professor Georg Pauli, Head of the Center of Biological Safety, Zentrum für Biologische Sicherheit (ZBS) Hochpathogene virale Erreger (ZBS 1) Robert Koch Institut, Berlin, Germany

Dr André D. Plantinga, Senior Project Manager, Vaccine Development, Netherlands Vaccine Institute (NVI), Bilthoven, The Netherlands

Professor Pilaipan Puthavathana, Senior Professor, Department of Microbiology, Faculty of Medicine, Siriraj Hospital, Mahidol University, Bangkok, Thailand

[1] Unable to attend

Dr Ciro de Quadros,[1] Director, Sabin Vaccine Institute, Washington DC, USA

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

Dr Li Ruan, Director, Biotech Center for Viral Disease Emergency Response, Institute for Viral Disease Control and Prevention, Chinese Center for Disease Control and Prevention, Beijing, China

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

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

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

Dr. Oyewale Tomori, Redeemer's Univeristy, Lagos, Nigeria

Dr Henda Triki, [1] Chief Laboratory of Clinical Virology, Institut Pasteur de Tunis, Tunisia

Dr Kummuan Ungshusak,[1] Director, Bureau of Epidemiology, Ministry of Public Health, Nonthaburi, Thailand

Advisers to the Committee

Dr Antonio Alcami, [1] Centro Nacional de Biotecnología (CSIC), Campus Universidad Autonoma, Madrid, Spain

Dr Kalyan Banerjee, Vice President, Maharashtra Association of Cultivation of Science, Agharkar Research Institute, Pune, India

Dr Peter D. E. Biggins, Head of IRS, DERA-CBD, CBY Systems, Porton Down, Salisbury, United Kingdom

Dr Mike Bray,[1] MD MPH, Medical Officer, Biodefense Clinical Research Branch, NIAID, National Institutes of Health, Bethesda, USA

Dr Patrick Celis, [1] European Agency for the Evaluation of Medicinal Products (EMEA), London, United Kingdom

Dr Inger K. Damon, Chief acting Poxvirus and Rabies Branch, Division of Viral & Rickettsial Diseases, National Center for Zoonotic, Vector Bone Disease, Center for Disease Control and Prevention, Atlanta, USA

Dr Karoline Dorsch, Executive Secretary, Swiss Expert Committee for Biosafety (EFBS/CFSB) Bern, Switzerland

[1] Unable to attend

Dr Joseph J. Esposito, Research Coordinator, Biotechnology Core Facility Branch, WHO Collaborating Centre for Smallpox and other Poxvirus Infections, Centers for Disease Control and Prevention, Atlanta, USA

Professor Daniel Garin, Head of Virology Unit, CRSSA Emile Pardé, Ministère de la Défense, Grenoble, France

Dr Dennis E. Hruby, Chief Scientific Officer, SIGA Technologies Inc. Corvallis OR, USA

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