

WHO Advisory Committee on Variola Virus Research

Report of the Ninth Meeting

Geneva, Switzerland
29 –30 November 2007



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Executive summary

The major accomplishments in the Variola virus research programme presented to the Committee were as follows:

- A new smallpox vaccine (ACAM 2000) has been licensed for use in one Member State.
- One attenuated smallpox vaccine (LC16m8), which has been licensed for use in one Member State since 1974, is being evaluated further in clinical trials for possible widespread use in smallpox prophylaxis.
- One vaccine (Imvamune®), which has the potential for use in individuals with contraindications to receiving 1st or 2nd generation vaccines, has performed satisfactorily in phase I and II clinical trials and will shortly be entering phase III trials.
- Two drugs displaying therapeutic activity in non-human primate models using Variola virus (cidofovir and ST-246), that target different proteins made at different stages during the Variola virus replication cycle, have been further developed and are available for emergency use.
- One drug, ST-246, which has passed phase I clinical trials, was used to treat an accidental, life-threatening case of eczema vaccinatum with subsequent recovery of the patient. Treatment with SR-246 was initiated sequentially after initiation of vaccinia immunoglobulin (VIG) and cidofovir. The potential of this drug for the treatment of related orthopoxvirus infections, such as monkeypox in man, is to be investigated.

The Advisory Committee noted that several time-limited research programmes, that had been approved by WHO, are nearing completion. The investigators involved in this research have been requested to submit final reports on completed research, or new proposals if further research is deemed necessary.

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1. Introduction

- 1.1 Dr David Heymann welcomed participants, particularly the new members, to the ninth meeting of the Advisory Committee on Variola Virus Research on behalf of the WHO Director-General. He drew comparisons with the work of this Committee and that concerned with the eradication of poliovirus and noted that reciprocal lessons could be learnt. He also noted that encouraging progress was being made in the area of research involving live Variola virus.
- 1.2 Dr Heymann concluded by stating that the World Health Assembly (WHA) had requested this Committee to undertake a review of the approved research programme in 2010 for presentation to the 64th WHA in 2011. This report would provide the basis for further discussions on the terms and timelines for the destruction of the remaining stocks of live Variola virus.
- 1.3 Dr Cathy Roth reminded the Committee that it was to advise WHO on the essential research which was required involving live Variola virus, and then to monitor the progress of this research. Members should reflect on both the science and the public health impact of the outcomes. The Advisory Committee then elected Professor Geoffrey Smith as chairman and Drs Robert Drillien and Peter Greenaway as rapporteurs.

2. Report of the WHO Secretariat

- 2.1 Dr Daniel Lavanchy reminded participants that the meeting report would be submitted to the WHO Director-General, then to the Executive Board and finally to the WHA. The report should remain confidential until the final version had been posted on the WHO web site.
- 2.2 Dr Lavanchy then stated that the major issue that had emerged since the last meeting of the Committee was the outcome of discussions at the last WHA. He reiterated the requests made to WHO and the Advisory Committee on Variola Virus Research, specifically:
 - A major review of ongoing essential research using live Variola virus and the plans and requirements for further essential research for global public health purposes is to be undertaken in 2010 in order to enable the 64th WHA in 2011 to reach global consensus on the timing of the destruction of existing Variola virus stocks. The precise methodology for conducting this review would be discussed at the Advisory Committee's next meeting.
 - The need to disseminate more widely, among all Member States, the outcomes and benefits of research using live Variola viruses.
 - The need to review the membership of the Advisory Committee. This had been done and a number of new members had been invited to attend the current meeting.
 - The requirement to report annually on progress in the research programme biosafety, biosecurity and related issues to the Health Assembly, through the Executive Board, as well as on the implementation of the recommendations of the

WHO Advisory Committee on Variola Virus Research, as accepted by the WHO Director-General.

- 2.3 Dr Lavanchy concluded by emphasizing that the WHA's requests were intended, firstly, to ensure that any research undertaken does not involve genetic engineering of Variola virus and, secondly, that the use and distribution of Variola virus DNA fragments are permitted only for purposes of research on diagnostics, treatment and vaccines.

3. Update on research proposals submitted to WHO

- 3.1 Dr Riccardo Wittek tabled a paper summarizing the research proposals approved or rejected by the Scientific Sub-Committee. Overall there have been 12 approved and 12 rejected work programmes. He noted that many of these projects were now coming to their anticipated completion dates and final reports should be submitted. He also noted that three new proposals had recently been received from the Centers for Disease Control and Prevention (CDC), Atlanta, United States of America, and that they will be evaluated according to the procedure agreed upon during the Committee's meeting in 2006.
- 3.2 Dr Wittek recognized that some of the completion dates may not be met and that those investigators affected should submit either a request for a time extension or a corresponding new proposal. He indicated that the Scientific Sub-Committee aimed to get all submitted proposals evaluated within 2 months of submission. If the work is completed, a final report must be submitted to the Committee. It was emphasized that final reports should describe progress against the proposed objectives. It was agreed that in future meetings the agenda would more closely reflect the ongoing research projects.

4. Update on Variola virus strains held in the repository of the United States of America

- 4.1 Dr Damon began her presentation by describing the restricted timelines for using the United States BSL-4 facilities for work with live Variola virus and how the repository functioned in terms of security and audit assessment. Between November 2006 and November 2007, there had been no change to the long-term inventory of 451 isolates, the majority of which were amplified originally on embryonated eggs and characterized during the final years of the smallpox eradication programme. The inventory of working stocks, which included 70 virus isolates (of which 45 had been fully sequenced), had shown 20 withdrawals for 4 different WHO approved projects; there had been no additions. The working stocks now need to be put into new boxes and seed pools of seed virus consolidated. An annual report on the strains held by the United States repository has been submitted to the WHO Secretariat.

5. Update on Variola virus strains held in the Russian collection

- 5.1 Professor Alexander Sergeev reiterated that the Russian collection contained 891 registered deposited items encompassing lyophilized and frozen cultures of 120 Variola virus strains and 17 biological specimens from smallpox patients. The inventory has remained unchanged since the last report. Renovations in the BSL-4 laboratory for

handling Variola virus have now been completed and further modernization of the repository is underway. He outlined the required security procedures needed to gain access to the repository, as well as the safety and emergency systems in place. He indicated that seven Asian isolates deposited in the Russian collection had been examined recently for viability in Vero cells and chicken embryos. Only three of these isolates were viable and one of them would be retained for further analysis.

6. Conservation of DNA and study of molecular evolution of Variola virus

- 6.1 Professor Sergei Shchelkunov indicated that the Russian State Centre for Research on Virology and Biotechnology (VECTOR) has preserved full-length DNAs of Variola virus from 29 strains. These samples are stored at 4 – 10 °C. Extended PCR amplicons covering the entire genome of 17 strains (apart from the termini) have been obtained and are preserved as alcohol precipitates. There are also 15 collections of cloned Variola virus DNA fragments stored as alcohol precipitates at -70°C. Documentation is available for all materials held within the repository and an updated report is to be submitted to WHO.
- 6.2 Phylogenetic studies on 21 Variola virus genomes have been performed using both restriction fragment length polymorphism (RFLP) and sequence analyses. Isolates from China, Japan and the Republic of Korea, appear to be similar to the West African strains, whereas Indian isolates appear to belong to several Asian phylogenetic subgroups. Studies on Variola virus phylogeny have now been completed. It was noted that these recent studies had been performed with DNA samples prepared in previous years and did not involve work with live Variola virus.

7. Review of the records which accompanied the Variola virus seeds comprised in the reference collection

- 7.1 An issue raised at a previous meeting was whether there was clinical information related to the strains held within the two repositories. Such information could provide a means to correlate virulence of the strains to their nucleotide sequence variability, where known. A study published by Sarkar and Mitra in 1967 had suggested that viruses isolated from patients with different clinical presentations of smallpox did indeed show differences in biological properties and differences in virulence when assessed in a variety of in vitro and in vivo systems. An analysis of the clinical records archived at WHO was therefore undertaken.
- 7.2 It was found that the archived records had been carefully stored and that there were several hundred case reports, but these were related to relatively few countries and outbreaks. Most of these reports contained little or no clinical information. This investigation therefore yielded no information to support or refute the original observations of Sarkar and Mitra.
- 7.3 It was also noted that viruses isolated from smallpox cases with different clinical presentations (haemorrhagic, confluent or sporadic lesions) did not breed true on secondary infection. Hence host responses probably represent an important component of severity of disease.

- 7.4 First hand experience from the eradication programme in India and Africa supported the observation that little clinical data had been collected during outbreaks. However, this may have been different in South America (Brazil) where it may be possible to access additional records. The Committee felt that this was an avenue worth pursuing and noted that the weakest link in epidemiological studies always appeared to be the collection of clinical data. This was an issue that should be brought to the attention of the wider infectious diseases networks, particularly in respect of emerging diseases.

8. Refinement of primate models using Variola to facilitate acceptance of countermeasures for smallpox

- 8.1 Dr Jahrling pointed out that many of the objectives of developing credible primate models of smallpox had now been achieved. There are two main models: first, monkeypox virus infection of cynomolgous macaques and second, infection of the same primate species with live Variola virus strains using intravenous inoculation, aerosol challenge or intratracheal exposure. Data generated during these studies have now been analyzed and have either been published or are under preparation for publication, but further work, directed towards gaining licensure of antiviral compounds, is still needed. It was recognized that other animal models (for example, ectromelia in mice, rabbitpox and camelpox in their respective hosts) could also produce useful data for bridging studies to authentic smallpox.
- 8.2 It was proposed that cytokine storms, which are not precisely defined and which occur as a result of an overreaction of the immune system, might influence some of the pathological consequences of orthopoxvirus infections. A number of immunological parameters are therefore being investigated to compare disease progression in different animal models so that the regulatory authorities can be satisfied that the disease process mimics the human condition sufficiently. This is essential if antiviral agents are to receive regulatory approval.

9. ST-246: drug development and human clinical safety studies

- 9.1 Dr Dennis Hruby presented recent progress on the development of an antiviral drug, ST-246 (SIGA Technologies Inc.). The development of ST-246 has been possible as part of the research agenda authorized by this Committee. The research has led to the identification of a compound that suppressed orthopoxvirus growth in vitro and is active in treating orthopoxvirus infections in animal models. ST-246 is an orally available, non toxic compound that is stable at room temperature. It has been used recently in a clinical case of eczema vaccinatum (see below). Initial dose ranging clinical studies are now in progress and it is anticipated that pivotal safety studies for regulatory approval will be undertaken. Studies in animal models have suggested that the drug levels needed to achieve therapeutic benefit can be achieved easily in humans with the proposed 14 day treatment protocol.
- 9.2 The Advisory Committee was informed that a pharmaceutical company (Albemarle) will undertake large scale synthesis of ST-246. This could ultimately allow a production capacity of roughly 25 million doses, and three small scale Good Manufacturing Practice (GMP) pilot lots have already been completed. Administration formats – capsules for daily oral administration, suspension preparations etc. – are being explored. Stability studies indicated that the compound is stable for 2 years at

room temperature and tests for longer-term stability are ongoing. Data on animal efficacy in different models, at different doses and at different times of administration, have been submitted to the United States Food and Drug Administration (FDA) as part of an Investigational New Drug (IND) submission.

- 9.3 The Advisory Committee was very encouraged by the findings presented and noted that funding from several agencies was being used to support this research. The Committee was also informed that results with ST-246 were sufficiently promising that small amounts of the drug were being stockpiled by the company for emergency, compassionate use. Work is in progress to determine if ST-246 can be used in immunocompromised individuals and pregnant women.

10. ST-246: animal efficacy studies

- 10.1 Dr John Huggins gave a brief overview of efficacy studies of ST-246. Based on activity in other multiple small animal models, oral ST-246 was evaluated in the Variola virus-cynomolgous monkey model of lesional smallpox that bears some resemblance to human disease.
- 10.2 The placebo group demonstrated typical disease with > 1250 pox lesions and 33% mortality. Oral gavage with ST-246 began 24 hours after infection, when all tissues showed extensive infection. Disease progression was halted, with no significant clinical or laboratory abnormalities. Virus levels in blood did not increase over pretreatment levels and virus was cleared in 6 days, versus 16 days for an alternate antiviral drug, cidofovir, based on historical data.
- 10.3 ST-246 was then evaluated using a monkeypox virus/cynomolgous monkey model. The placebo treated group demonstrated typical disease with > 1500 pox lesions and 100% mortality. Oral gavage treatment with ST-246 began 1 day after infection, when all tissues showed extensive infection. This treatment halted disease progression and no significant clinical or laboratory abnormalities were recorded.
- 10.4 Dose seeking studies of oral treatment of cynomolgous monkeys infected with a uniformly lethal dose of monkeypox virus were initiated 3 days after infection when primates showed signs of clinical disease and 1/3 had typical poxvirus lesions, i.e. a point when a clinical diagnosis could easily be made. At this time viral replication had progressed to the point that all organs had high viral burdens. All doses (300 to 3 mg/kg) resulted in protection from death. ST-246 treatment also reduced lesion formation and viral load significantly, with no obvious toxicity. Ongoing ascending multiple dose human clinical studies, designed to establish the human dose, and similar pharmacokinetic studies in cynomolgous monkeys, indicate that the human dose that provides the same drug exposure as the primate dose of 30 mg/kg is achievable, and that this dose is 10-fold higher than that required to protect primates.
- 10.5 ST-246 is orally bioavailable with excellent pharmacokinetic parameters. Preclinical development is complete and the United States FDA has granted an IND, Fast-Track status and Orphan Drug Designation. Human clinical studies with ST-246 are underway and New Drug Application (NDA)-enabling studies are in progress. Ongoing clinical studies show that ST-246 appears safe and well-tolerated when administered orally as a single dose to healthy normal volunteers in a fasted (500 to 2000 mg) or non-fasted

(1000 mg) state. Human twenty-one day dosing studies are nearing completion at oral doses of 250, 400 and 800 mg/day in fed adults.

- 10.6 It was noted that ST-246 might be used to treat some smallpox vaccine adverse reactions, and that with CMX100 (the oral lipid conjugate prodrug of cidofovir), the requirement of having two drugs that inhibit Variola virus replication by acting on different targets could be satisfied. Continued attention is also being paid to analogues of Gleevec/imatinib (Gleevec®, Glivec®), a tyrosine kinase inhibitor, for its potential in treating smallpox.
- 10.7 The Committee noted that additional assessments of antiviral agents in non-human primate models of smallpox, under Good Laboratory Practice conditions, are limited by the availability of BSL-4 containment facilities.

11. The critical role of the viral TNF receptor in mousepox

- 11.1 Dr Antonio Alcami reminded the Committee of data published by his team last year describing a Variola virus soluble TNF receptor which also displays chemokine binding activity (CrmB). The Variola virus encoded chemokine receptor domain within CrmB inhibited chemokine activities that could exert their action at sites of viral entry such as mucosal surfaces and the skin.
- 11.2 A related protein encoded by the ectromelia virus genome (CrmD) displayed similar activity to Variola CrmB and this finding has provided an opportunity to investigate its role in pathogenesis in a mouse model. A knockout mutant of the ectromelia virus CrmD gene is highly attenuated in the mouse. Infection with the knockout mutant entails extensive local inflammation at the initial infection site, unlike infection with the parental ectromelia virus, demonstrating the role of CrmD in blocking this process. These data demonstrate the importance of soluble cytokine receptors in systemic orthopoxvirus infections and draw our attention to their potential role in smallpox in humans.

12. Human B cell responses following smallpox vaccination

Dr Koert Stittelaar reported on recent work conducted by his team to assay for the B cell response induced upon a booster smallpox vaccination in laboratory workers. The assay specifically scored the number of B cells in peripheral blood mononuclear cells (PBMC) that were capable of secreting antibodies against Vaccinia virus. The assay allowed the determination of the kinetics of appearance and the following decay in the number of virus-specific B cells, and was reported to be more sensitive in detecting an immune response to revaccination than an ELISA assay for virus-specific antibodies. The assay was considered to be more cumbersome than more commonly used methods and would only be applicable on a limited scale.

13. Immunogenicity studies of candidate DNA vaccines based on Variola virus genes

- 13.1 Professor Sergei Shchelkunov described experiments carried out by his team to determine which Variola virus DNA coding regions could be included in a vaccination strategy based on naked DNA. Eight distinct open reading frames were selected and positioned downstream of one of two commonly used promoters for expression in

animal cells. Injection of two DNA constructs into mice induced anti-orthopoxvirus antibodies but only one DNA construct comprising the F8L gene, the equivalent of the Vaccinia virus D8L gene, induced both a humoral and a cellular response - by analogy with Vaccinia virus, the Variola virus F8L gene should encode a target of neutralizing antibodies on the intracellular mature virus (IMV) particle. Three successive inoculations of DNA encoding F8 into mice by the intraperitoneal route, in the case of one kind of F8 coding plasmid, or by the intradermal route, in the case of another kind of F8 coding plasmid, were able to partially protect mice from a lethal challenge infection with ectromelia virus.

- 13.2 This work confirms the findings of previous studies from other laboratories which demonstrate that DNA vaccination can be an effective means of prophylaxis in orthopoxvirus model systems, although the potential for such a strategy for vaccinating humans is uncertain.
- 13.3 Dr Huggins reminded the Committee of work performed previously in collaboration with Dr Moss's team which demonstrated the induction of humoral immunity by a protein subunit vaccine comprising two Vaccinia virus proteins (A33 and B5) of the extracellular enveloped virus (EEV) and one Vaccinia virus protein (L1) of IMV. Monkeys were partially protected from a monkeypox virus challenge after 4 subsequent injections with this combination but the level of protection was weaker than the one achieved after vaccination with modified Vaccinia virus Ankara (MVA) as more viral lesions and a higher viral load were noted than obtained after vaccination with MVA.
- 13.4 Dr Huggins also recalled work previously reported by Jay Hooper and colleagues which employed a combination of 4 plasmids encoding Vaccinia virus proteins, and a regime of 4 vaccinations over a 4 month period, to vaccinate monkeys against monkeypox virus. Under these circumstances, the monkeys survived the challenge infection but there was still significant morbidity. It was pointed out that after DNA vaccination with orthopoxvirus genes there appeared to be a good correlation between the serological response and protection from death, but not between the serological response and protection from morbidity.

14. Efficacy of MVA and Dryvax vaccines to induce Variola virus neutralizing antibodies

- 14.1 Dr Damon reported on experiments conducted at the CDC maximum containment laboratory in 2006 using live Variola virus as the target of plaque reduction neutralization tests (PRNTs) in evaluation of MVA and Dryvax® vaccination regimes. In 2007, the data were analyzed with respect to 60% neutralization, 90% neutralization, geometric mean titers and 4-fold and 8-fold increases in neutralization titers. MVA vaccination regimes performed in a non-inferior manner and, in some analyses, the level of neutralizing antibodies appeared higher than after vaccination with Dryvax®.
- 14.2 Additional analyses compared Variola virus PRNTs performed at the CDC with Vaccinia Dryvax® and MVA PRNTs obtained at the University of Saint Louis after vaccination with Dryvax® or MVA, in an effort to compare neutralization titers using these different orthopoxviruses as PRNT targets. No linear correlation was found between individuals' different PRNT responses against Vaccinia (Dryvax®), MVA and Variola virus (strain Solaiman). It was suggested that these data imply that Variola virus PRNT responses may be important for evaluating smallpox vaccines, especially if

the vaccination regimen does not elicit the historical correlate of successful vaccination, i.e. the “take”.

15. Update on the attenuated MVA vaccine

- 15.1 Dr Paul Chaplin presented an update on the MVA based smallpox vaccine produced by the Bavarian Nordic company under the trade name Imvamune®. After a brief reminder of the historical use of MVA as a prevaccine against the adverse effects of the traditional smallpox vaccine, more recent preclinical and clinical data to evaluate MVA as a stand alone smallpox vaccine were reviewed.
- 15.2 In preclinical studies, MVA was safe in highly immunocompromised AGR129 mice and conferred complete protection against a variety of animal orthopoxvirus infections (vaccinia WR, cowpox virus and ectromelia virus in mice; monkeypox virus in monkeys). In the mouse model, MVA induced a more rapid immune response than Dryvax®, which was considered to be due to the higher doses of the MVA vaccine employed. Mice were also protected from a challenge with Vaccinia virus infection 3 days after MVA vaccination, but more time was required after Dryvax® vaccination. This difference correlated with the increased immune response induced by MVA. Mice lacking the TLR 9 receptor were more susceptible to ectromelia virus infection than normal mice and they could be protected by MVA vaccination on the day of challenge with ectromelia virus.
- 15.3 Dr Chaplin reported that phase I and II clinical studies have so far been carried out with MVA on 1500 volunteers including people with allergies, skin conditions and HIV, and no adverse reactions were recorded. Notably, no evidence of myopericarditis was observed. Equivalent levels of neutralizing antibodies were observed in volunteers vaccinated with MVA or Dryvax® 28 days or one year post vaccination. Lesions induced by a secondary smallpox vaccination with Dryvax® were milder and contained less virus in volunteers who had received a primary MVA vaccination than those who had not previously been vaccinated.
- 15.4 A frozen liquid formulation of the MVA vaccine has been produced, tested for stability, and phase III clinical trials are being initiated.

16. Epidemiology and non-clinical/clinical evaluation of the LC16m8 vaccine

- 16.1 Professor Isao Arita presented the history of the use of the LC16m8 smallpox vaccine in Japan and the more recent studies performed with this Vaccinia virus strain. It was recalled that LC16m8 was licensed in Japan in 1975 as a smallpox vaccine and that it had been used several decades ago in 90 000 infants. Vaccination was followed by smaller indurations and less fever than with the traditional smallpox vaccines, and there was no reported encephalopathy in those examined. The take rate and level of induction of neutralizing antibodies was comparable to the Dryvax® vaccine.
- 16.2 Dr Yokote from The Chemo-Sero-Therapeutic Research Institute (KAKETSUKEN), Kumamoto, Japan, described the studies regarding the attenuated smallpox vaccine LC16m8. In Japan, LC16m8 is a licensed drug product, and post marketing surveillance of this product has been conducted since 2005. In the USA, an IND for LC16m8 has been submitted, and phase I/II clinical study has been completed.

- 16.3 In recent clinical studies, LC16m8 was inoculated into more than 8000 adults in Japan, and in 125 adults in the USA. Regarding safety, 3000 subjects were initially evaluated for safety: 2 subjects were suspected to have adverse events related to vaccination but none was severe. LC16m8 showed a take rate of more than 95% and a sero-conversion rate of more than 94%, results that are comparable to data obtained in the past in infants, and also to data recently obtained in adults. Challenge studies in mice and monkeys showed the same protection when compared to a vaccine based on the Lister strain.
- 16.4 The LC16m8 vaccine was highly attenuated in rabbits and showed considerably reduced neurovirulence upon brain inoculation into suckling mice or monkeys. The vaccine was also safe in immunocompromised SCID mice immunized by tail scarification or intraperitoneal inoculation. In addition, vaccination against Vaccinia virus WR strain could be achieved in MHC II deficient mice or in combined MHC I and MHC II deficient mice, suggesting that natural and specific cell immunity are involved in protection in the early stages.
- 16.5 Currently, the LC16m8 vaccine is manufactured as a heat stable freeze-dried preparation that can be used at doses and can be administered in a manner similar to the traditional smallpox vaccine. Annual production capacity is 80 million doses. Currently, validation of the production facility is ongoing.

17. Regulatory issues about licensing 3rd generation vaccines

- 17.1 Dr Michael Merchlinsky reviewed the current status of the requirements for licensing third generation smallpox vaccines. He recalled that third generation vaccines include attenuated Vaccinia virus strains as well as subunit vaccines made from viral proteins or DNA. The major problems faced in the development of such vaccines lie in the absence of a small animal model for smallpox that would allow a large number of animals to be handled, and the lack of knowledge of the correlates of protection against human smallpox. It was stressed that candidate vaccines should be compared to the traditional vaccines with regards to the immune response and protection they induce in a variety, if not all, of the orthopoxvirus animal models available. It appeared, however, that an animal model employing live Variola virus will not be mandatory for licensing a third generation vaccine if sufficient data had been obtained from a large body of evidence using other orthopoxvirus animal models.
- 17.2 During discussion of the presentation, Dr Michael Merchlinsky indicated that the FDA-CBER (United States Food and Drug Administration-Center for Biologics and Research) would find it very useful, during the evaluation of candidate 3rd generation vaccines, to evaluate the induction of serological responses to Variola virus. A few members of the Committee questioned whether such assays using live Variola virus are indeed necessary and whether they could instead be replaced by serological responses to other orthopoxviruses or antigens thereof. The discussion also highlighted the difficulty of further use of 1st and 2nd generation vaccines for comparative purposes in view of the adverse reactions they may cause.
- 17.3 It was pointed out that the European Medicines Agency (EMA) had provided guidelines for the development of 2nd generation smallpox vaccines that would not

require the use of live Variola virus in animal protection studies, and that the policy for the development of vaccines produced by genetic engineering and/or gene transfer technologies would be addressed in the future.

- 17.4 With regards to 2nd generation smallpox vaccines, the Committee was reminded that one such product (ACAM2000™, Acambis) had been licensed for use in the USA during the year 2007.

18. Preliminary characterization of a collection of monoclonal antibodies, generated against expressed Vaccinia virus proteins, and their recognition of Variola virus

18.1 Dr Inger Damon presented the analysis of a panel of monoclonal antibodies raised against two Vaccinia virus EEV proteins (A33, B5) and one IMV protein (L1). The anti-L1 antibodies neutralized Vaccinia virus and Variola virus IMV at relatively low concentrations, and some anti-L1 antibodies performed better in PRNT against Variola virus than against Vaccinia virus. At high concentrations, some B5 antibodies inhibited Variola plaque formation. Antibodies against the B5 protein inhibited virus spread in a comet formation assay; this included one monoclonal antibody shown not to bind the Variola homolog in a BIACore™ assay.

18.2 The data indicated clear cross reactivity of the antibodies raised against Vaccinia virus proteins against Variola virus proteins as might be expected, but also demonstrated the differences between results obtained with experiments using expressed Variola proteins and authentic virus. The data suggested that the antibodies studied could be employed in immune capture assays for Variola or other orthopoxviruses. Another potential application of such antibodies would be as a replacement of VIG, and/or as an adjunct to vaccination, although such applications would require prior humanization of the antibodies.

19. Use of VIG, cidofovir and ST-246 in the treatment of a severe case of eczema vaccinatum

19.1 A report of treatment of a case of eczema vaccinatum was given. A 28-month-old male, with a history of atopic dermatitis, presented with fever and extensive rash. Medical history revealed that the father, a member of the United States army, had received a smallpox vaccination 21 days before visiting his family.

19.2 The possibility of eczema vaccinatum was considered when the mother developed facial lesions and systemic conditions after the child was hospitalized. PCR analysis of clinical specimens confirmed a Vaccinia virus infection in the child. Antiviral immunoglobulin (VIG) administration was initiated at maximum dose levels to achieve tissue penetration (11 doses at 24 000 units/Kg). New lesions developed despite the use of VIG.

19.3 A single systemic dose of cidofovir was administered, and as the clinical condition of the child continued to deteriorate, permission to treat with ST-246 was sought. This was granted, and the drug was administered for a two-week period using a naso-gastric tube. Slow improvement resulted with skin lesions coalescing and flattening. Scabs were monitored by PCR for the presence of virus, but these were only considered negative at 36 days post hospitalization when the child was released from contact isolation.

- 19.4 A number of lessons were learned as a result of this case report. First, it may not have been prudent to vaccinate the father and then to allow interaction with the affected child 21 days later. Second, the availability of images of the rash should not be underestimated as a diagnostic tool, and “remote access” communication, via conference calls, can be quite effective in rapidly disseminating information, and acquiring additional (therapeutic) resources. Third, additional research is needed into effective therapies for eczema vaccinatum. Last, access to real time laboratory generated data is essential for patient management.
- 19.5 During discussion it was noted that there has been no clinical trial for the use of VIG and that, given the properties of ST-246, drug therapy should be considered as an early treatment option. It was also noted that a large amount of resources had been deployed to treat just one child, and that this was not sustainable or applicable, in particular, to developing countries.

20. Preliminary results from the study of the natural history of human monkeypox in the Democratic Republic of the Congo

- 20.1 Dr Huggins reported on behalf of the principal investigator Dr Muyembe, who was unable to be present at the meeting, on a clinical study being conducted jointly by the Democratic Republic of the Congo (institutions: L'Hôpital Général de Référence de Kole, Institut National de Recherche Biomédicale (INRB), Kinshasa School of Public Health), and the United States Army Medical Research Institute of Infectious Diseases. The study is being conducted at the same hospital where, from 1981 to 1986, WHO conducted the original monkeypox studies. The study is designed to evaluate the clinical course of monkeypox in patients hospitalized and treated according to standard practices at Kole Hospital, to provide a better description of human monkeypox utilizing newer tools. The study involves an extensive clinical history, daily physical examination and will follow the course of disease. Laboratory studies include complete blood cell count, serum chemistry profile, urinalysis, and viraemia by onsite quantitative real time TaqMan® PCR diagnosis. Additional studies will include antibody kinetics, host cytokine response and determination of concomitant infections.
- 20.2 This is a preparatory study designed to train hospital staff in good clinical practices, build hospital infrastructure and obtain the information necessary to design and propose a limited clinical trial of ST-246, once adequate human safety studies have been conducted in the United States, to assure the drug safety. The study has also improved the capabilities of the country reference laboratory (INRB) to provide real time PCR diagnosis of monkeypox in Kinshasa.

21. Composition of the Scientific Sub-Committee for the evaluation of research proposals

- 21.1 Dr Riccardo Wittek reminded the Advisory Committee of its previous recommendation that up to one third of the members of the Scientific Sub-Committee should be rotated annually. In addition, because of possible conflicts of interest, it had been decided that staff from the Collaborating Centers should be excluded from membership of this Sub-Committee.

- 21.2 In accordance with this recommendation, Dr Wittek tabled a revised membership of the Scientific Sub-Committee. This new composition was noted by the Committee.

22. Review of the research work done by laboratories that have obtained limited regions of Variola virus DNA with WHO approval

- 22.1 As part of its obligation to oversee research activities using portions of Variola virus DNA, the WHO Secretariat presented some preliminary data from a survey of laboratories known to be engaged in this research. The subject laboratories were identified through WHO records of approved requests for Variola virus DNA fragments, CDC records of distributions of Variola virus DNA fragments, and publications related to Variola virus DNA fragments since 1994. Although one of the Committee members expressed concern about the methodology used in developing the preliminary data, the Committee welcomed this effort. The Committee was of the view that WHO should continue to have access to up-to-date information on the use and distribution of Variola virus DNA fragments, which is essential for the confidence of the wider public health community. The Committee recognized that further steps were needed to complete the work, and it recommended that the Secretariat continue its efforts to increase the awareness of the regulations and guidelines governing the use and distribution of Variola virus DNA.

23. Variola virus DNA: third party transfers

- 23.1 Following on from the previous discussion, Dr Riccardo Wittek introduced a discussion on the current recommendations concerning the distribution, handling and synthesis of Variola virus DNA. A paper summarizing these recommendations was tabled.
- 23.2 This precipitated a wide ranging discussion of the issues. A general consensus emerged that the wording behind the current recommendations and guidelines should not be changed. The major problem identified was one of wider dissemination and communication of the existing recommendations and guidelines. In addition, it was felt that the general principles behind these regulations should be clarified and emphasized.
- 23.3 These general principles revolve around the fact that only two laboratories are authorized to work with live Variola virus, that attempts to reconstitute live virus in vitro are forbidden, and that Variola virus DNA fragments should not be handled in laboratory environments where other orthopoxviruses are handled. The main objective is to prevent unregulated dissemination of sensitive materials for potential misuse.
- 23.4 A major issue in this regard was considered to be the third party transfer of DNA fragments. All agreed that this requires authorization by WHO and that this should be controlled through the Material Transfer Agreements between the distributing and receiving laboratories (with copy to WHO). This was considered important for WHO in order to have oversight of the distribution of all Variola virus DNA fragments.
- 23.5 The Advisory Committee was of the view that there should be proactive dissemination of the current regulations, recommendations and guidelines relating to the use of Variola virus and Variola virus DNA fragments (WHO/CDS/BVI/94.3, WHO/CDS/CSR/ARO/2005.4). It was recommended that a summary document on these issues should be produced by the WHO Secretariat. This should be based on the

paper tabled by Dr Wittek and a similar document available from the CDC. The document produced should be comprehensive but relatively short, understandable and accessible. Once produced, every participant at this Advisory Committee meeting, as well as the Secretariat, would take responsibility for its wider dissemination to a range of organizations and national and international agencies. These should include relevant professional societies, specialist and generalist scientific and medical journals, relevant government departments, funding agencies and biotechnology companies.

24. Information on the operational procedures for the release of the WHO vaccine stockpile, and operational aspects for the establishment of regional surge diagnostic capacity

- 24.1 Dr Daniel Lavanchy from the WHO Secretariat updated the Committee on the current status of the WHO stockpile of smallpox vaccine. This stockpile comprises 1st generation vaccines already available in Geneva (2.5×10^6 doses) and vaccines pledged to WHO by Member States (31×10^6 doses). Targets for the stockpile include a doubling of the amount of vaccine in Geneva and an increase to 195×10^6 pledged doses from Member States. In response to questions concerning the availability of new 2nd and 3rd generation smallpox vaccines, the WHO Secretariat mentioned that the Organization would consider accepting into the stockpile any new vaccine that had demonstrated its utility and safety, after adequate consultation with experts and with regulatory agencies from Member States. It was suggested that WHO might actively solicit the safer, new generation vaccines for emergency use because of the large number of immunosuppressed people in the world's population. With a few exceptions, most members of the Committee agreed that it would not be necessary for countries with limited resources to invest in the local production of smallpox vaccines, in line with the views previously expressed by the *Ad Hoc* Committee on Orthopoxvirus Infections.
- 24.2 The Secretariat reported on the initial steps being taken to establish a virtual network of laboratories, able to conduct frontline differential diagnosis of smallpox safely and rapidly, with the understanding that final virus isolation and identification would be performed in one of the two WHO smallpox Collaborating Centres. The purpose of this network will be to ensure access to validated diagnostic procedures and to maintain standards of quality in all WHO Regions.

Annex 1. Agenda

Ninth Meeting of the WHO Advisory Committee on Variola Virus Research

28 and 29 November 2007

Executive Board Room , WHO Headquarters, Geneva, Switzerland

Agenda

28 November 2007

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| 9:00 – 9:15 | Opening – D. Heymann
Election of chair & rapporteur |
| 9:15 – 9:30 | Report of the secretariat – D. Lavanchy |
| 9:30 – 9:45 | Update on research proposals submitted to WHO – R. Wittek |
| 9:45 – 10:00 | Update on Variola virus strains held in the US repository – I. Damon |
| 10:00 – 10:15 | Update on Variola virus strains held in the Russian collection – A. Sergeev |
| 10:15 – 10:30 | Conservation of DNA and study of molecular evolution of Variola virus – S. Shchelkunov |
| 10:30 – 11:00 | Tea/Coffee Break |
| 11:00 – 11:15 | Review of the records which accompanied the Variola virus seeds comprised in the reference collection - P. Jahrling |
| 11:15 – 11:45 | Refinement of Primate Models using Variola to Facilitate Acceptance of Countermeasures for Smallpox – P. Jahrling |
| 11:45 – 12:15 | ST-246: drug development and human clinical safety studies – D. Hruby |
| 12:15 – 13:15 | Lunch |
| 13:15 – 13:45 | ST-246: animal efficacy studies – J. Huggins |
| 13:45 – 14:00 | Discussion |
| 14:00 – 14:30 | Preliminary results from the study of the natural history of human monkeypox in the Democratic Republic of the Congo – T. Muyembe |
| 14:30 – 14:45 | The critical role of the viral TNF receptor in mousepox: implications for the development of new smallpox vaccines – A. Alcami |
| 14:45 – 15:00 | Human B cell responses following smallpox vaccination – K. Stittelaar |
| 15:00 – 15:15 | Immunogenicity studies of candidate DNA vaccines based on Variola virus genes – S. Shchelkunov |

- 15:15 – 15:30 Analysis of data looking at the efficacy of MVA to neutralize Variola virus (control: Dryvax) – I. Damon
- 15:30 – 15:45 Update on the attenuated MVA vaccine – L. Wegner
- 15:45 – 16:00 Epidemiology and clinical evaluation of the LC16m8 vaccine – A. Arita
- 16:00 – 16:15 Evaluation of the LC16m8 strain through animal models including immune compromised mouse – H. Yokote
- 16:15 – 16:45 **Tea/Coffee Break**
- 16:45 – 17:00 Regulatory issues about licensing 3rd generation vaccines – M. Merchlinsky
- 17:00 – 17:30 Discussion: correlates of immunity; what work requiring live Variola virus is necessary for licensing of 3rd generation vaccines?
- 17:30 – 17:45 Preliminary characterization of a collection of monoclonal antibodies generated against expressed Vaccinia proteins, and their recognition of Variola virus – I. Damon
- 17:45 – 18:00 Development of fully human monoclonal antibodies neutralizing pathogenic orthopoxviruses – A. Sergeev
- 18:00 – 18:15 Use of VIG, cidofovir and ST246 in the treatment of a severe case of eczema vaccinatum – I. Damon
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- 18:30 – 19:30 Social event at the WHO main cafeteria (Crystal Room, Main Cafeteria)

DAY 1 CLOSES

29 November 2007

- 9:00 – 9:15 Composition of the technical subcommittee for the evaluation of research proposals – R. Wittek
- 9:15 – 9:45 Review of the research work done by laboratories that have obtained limited regions of Variola virus DNA with WHO approval – Zhenqiang Bi
- 9:45 - 10:15 Discussion
- 10:15 – 10:45 **Tea/Coffee Break**
- 10:45 – 11:00 Variola virus DNA: third party transfers? – R. Wittek
- 11:00 – 11:15 Discussion
- 11:15 – 11:30 Update on the operational procedures for the release of the WHO vaccine stockpile and operational aspects for the establishment of regional surge diagnostic capacity – D. Lavanchy
- 11:30 – 12:00 Discussion
- 12:00 – 13:30 **Lunch**
- 13:30 – 13:45 Miscellaneous
- 13:45 – 15:30 General discussion and preparation of draft recommendations
- 15:30 – 16:00 **Tea/Coffee Break**
- 16:00 – 17:00 General discussion and preparation of draft recommendations (cont.)

MEETING CLOSES

Annex 2. List of participants

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