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WHO Advisory Committee on Variola Virus Research

Report of the Eleventh Meeting

Geneva, Switzerland
4–5 November 2009

GLOBAL ALERT AND RESPONSE

World Health Organization

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Executive summary

The major accomplishments in the WHO variola virus programme were as follows:

- WHO smallpox vaccine emergency stockpile of 32.6 million doses was established, well in excess of the original target of five million. Four individual Member States have pledged 27 million doses to be given in case of additional needs.

- In light of the 2011 review process on smallpox research, the Committee had agreed that it would produce a report based on a series of reviews and these would be submitted to an external committee that was independent of both WHO and its Advisory Committee for review. The Advisory Committee considered and discussed six preliminary reviews.

- The potential usefulness of wild-caught prairie dogs (*Cynomys ludovicianus*) as a model for human smallpox was investigated. Because of the lack of overt illness, the prairie dog was not considered to be a good animal model for variola virus infections.

- Work continues in investigating protein-based diagnostics and the development of point-of-care assays that are simple to use, stable, robust and easy to interpret.

- The potential reservoirs of, diagnostics for, and the epidemiology of cowpox virus infections in Germany was reported, but cases have been reported in other European countries as well. Human infections through zoonotic transmission have been documented. It is believed that rodents are the reservoir. It was noted that the cowpox virus infections in rats may be a promising model of orthopoxvirus pathogenesis.

- The Committee was presented with a comprehensive review of antiviral agents which have shown anti-variola virus activity (cidofovir, ST-246 and CMX001). These compounds have obtained Investigational New Drug (IND) status from the US Food and Drug Administration (FDA). The Committee recalled that capability to perform work with live variola virus must be maintained at least until two anti-variola drugs with different mechanisms of action have gained regulatory approval.

- The access and preservation of the WHO archives of the Smallpox Eradication Programme was discussed. Work is under way to convert all the materials into a digital format which will allow full text searching.

- The Committee reviewed the risks and benefits of vaccinating with smallpox vaccine health-care workers exposed to monkeypox. The Committee decided that vaccination of health-care workers should be given to HIV negative health-care workers because of the risks associated with exposure to monkeypox virus. Vaccination after an outbreak was detected would not provide time for screening for HIV and would be too slow to offer optimal protection.

Content

1. Report from the Secretariat

1.1. The WHO Advisory Committee on Variola Virus Research met on 4 and 5 November 2009 with Professor G.L. Smith as Chairman and Mr D.W. FitzSimons as Rapporteur.

1.2. Dr K. Fukuda opened the proceedings, recalling the importance of the eradication of smallpox for current work on the eradication of other diseases. He outlined the process for responding to the request of the Health Assembly in resolution WHA60.1.

1.3. Dr D. Lavanchy recalled that the report of the tenth meeting had been noted by the Sixty-second World Health Assembly in May 2009.[1] He reported on the successful inspection of the smallpox repository and containment facilities at the Centers for Disease Control and Prevention (CDC) in Atlanta, Georgia, United States of America, in March 2009 and indicated that, for the first time, the report is publicly available on the WHO web site.[2] The inspection of the smallpox repository and containment facilities at the VECTOR laboratory in Novosibirsk, Russian Federation, is scheduled for December 2009.

1.4. A WHO smallpox vaccine emergency stockpile is stored securely in Switzerland; it includes 32.6 million doses, well in excess of the original target of five million. Potency testing is currently being conducted at the National Institute of Virology in the Netherlands. Donations to the stockpile are still welcome, including newer generation vaccines, bifurcated needles and other materials. Standard operating procedures for release and distribution of this stockpile have been prepared. Four individual Member States have pledged 27 million doses to be given in case of additional needs, and similar standard operating procedures are being drafted with these four Member States. The ad hoc Committee on Orthopoxvirus Infections recommended an emergency stockpile of 200 million doses.

1.5. Later in the course of the meeting Dr D. Lavanchy proposed new members for the Committee's scientific subcommittee, which the Committee approved.

2. Institute of Medicine report

2.1. Dr D. Ulaeto presented a brief overview of the report from the United States National Academy of Sciences Institute of Medicine's Committee on the Assessment of Future Research Needs for Live Variola Virus,[3] in the preparation of which he was the only representative of the WHO Advisory Committee to participate. The report was released simultaneously with the Advisory Committee's meeting. The Institute's Committee concluded that live variola virus was required for the development of therapeutics and assessment of resistance to these drugs and for the development of vaccines that do not manifest a "take". As the only known reservoir of variola virus is man, it recommended that CDC undertake a comprehensive evaluation of the work done to date on the non-human primate model of variola pathogenesis, in conjunction with an expert panel knowledgeable about poxviruses and animal models of viral infection. The objective

[1] Document WHA62/2009/REC/3, summary record of the fourth meeting of Committee B, section 2B.
[2] http://www.who.int/entity/csr/disease/smallpox/Report_2009_CDC_WHO_Inspection.pdf
[3] IOM, Live Variola Virus: considerations for continuing research: http://www.iom.edu/en/Reports/2009/LiveVariolaVirusContinuingResearch.aspx

would be to identify ways in which the predictive value of the model for testing therapeutics and vaccines might be improved. It stated that further genome sequence analysis would be useful but was not essential. It also recommended to explore the use of functional genomics in order to improve understanding of the origin and development of variola virus and to advance the development of new strategies for safe and effective therapy.

2.2. The Chairman recalled that the Advisory Committee had repeatedly agreed that further sequencing was not justified for public health. As the Advisory Committee is undertaking a comprehensive review of variola virus research and the resulting report will be reviewed by an independent panel of experts, the Advisory Committee will evaluate at its next meeting whether further evaluation of the non-human primate model of variola virus infection is deemed appropriate.

3. Update on research proposals

3.1. Dr R. Drillien reported that in the course of 2009 seven new proposals for research had been received, three from CDC and four from VECTOR (the latter submitted to the subcommittee only recently). The CDC proposals were approved for one year and covered protein-based diagnosis, diagnostic materials and assays for less reactogenic vaccines.

4. Review papers

4.1. The Committee had previously agreed that it would produce a report based on a series of reviews and Dr D. Lavanchy outlined the process for reviewing manuscripts prepared by Committee members for that purpose. That report would be submitted to an external committee that was independent of both WHO and its Advisory Committee for review and assessment of the achievements made over the past 10 years, identification of gaps that remain, and determination of the outcomes for public health. The composition and membership of the external committee were being decided. The Advisory Committee considered and discussed the following six reviews.

4.2. Dr I. Damon summarized the detailed information that had been collated on the status of the collection of strains of virus and nucleic acid samples in both the American and Russian repositories (CDC and VECTOR). The Committee suggested harmonization of the presentation of the data and that more precise quantitative information should be provided to the Committee.

4.3. Dr Damon also introduced a further collaborative review of laboratory diagnosis of smallpox and variola virus, covering aspects of clinical signs and symptoms, collection and handling of specimens, and the range of methods used. These methods included electron microscopy, virus isolation, DNA-based methods (e.g. restriction fragment length polymorphism, polymerase chain reaction-based approaches, and oligonucleotide microarray assays), sequencing, protein-based assays and serological antibody tests. One suitable test kit is commercially available for research purposes only, but is not licensed for diagnosis. In discussion, concern was expressed about the lack of broad access to licensed diagnostic tests in most Member States. A possible role

for WHO would be to investigate the pre-qualification procedures.[4] The core capacities required under the International Health Regulations (2005) might be a lever for increasing availability of diagnostic test kits.

4.4. Dr G. McFadden presented a multi-author review of variola genomics, covering the sequencing of 49 variola virus strains (the data have been published in the public domain), [5] the virus's evolution over time, poxvirus genome technologies, and considerations for the containment of variola virus genomes. He noted that sequencing had not included the very short terminal hairpin sequences of the genome, but it was thought that knowledge of these noncoding sequences, which are similar to those of other orthopoxvirus terminal hairpins, was not essential. He highlighted the major and rapid advances made over the past 10 years in the technologies of viral genome sequencing, synthesis and informatics, and concluded that the synthesis of full-length variola virus genomes and the creation of live orthopoxviruses is now technically feasible. Because WHO's current approach to control of variola virus is based on restriction of live variola virus to only the two WHO reference laboratories and control of distribution of individual genes such that no laboratory has more than 20% of the variola genome, the development of new and simple synthetic technology will in the future no longer assure that full-length variola virus genomes could only exist in the two WHO reference labs. Members of the Committee stressed that Member States need to be aware of these advances in synthetic biology and their implications, in particular the need to review policies on biocontainment. These advances necessitate the continued evaluation of existing guidelines on work with live variola virus and variola virus DNA. Ethics and biosafety committees should be aware of, and responsible for, implementing guidelines at the local level. Even if poxvirus genome synthesis projects were to be undertaken, their application to the creation of a synthetic variola virus is prohibited by existing regulations and would be considered a crime against humanity.

4.5. Dr A. Alcami presented the joint review on vaccines against smallpox, from the history of vaccination, the origin of vaccinia virus and the WHO Smallpox Global Eradication Programme. He went through the different generations of vaccines, from the first-generation vaccines generated in live animals, through second-generation vaccines produced in tissue culture and third-generation vaccines produced in tissue culture and characterized by attenuating mutations occurring during cell culture passage, to fourth-generation vaccines produced by genetic engineering technology. It was emphasized that first- and second-generation vaccines were licensed and highly effective, the first-generation vaccines having been used in the eradication of smallpox. The review also considered vaccination after exposure to smallpox before outlining the future challenges, including standards of vaccines manufactured to replenish the current stocks, the need for safer vaccines and the difficulty to show that newly developed vaccines induce protective immunity in humans and to test their efficacy against natural disease. Several promising candidate vaccines with fewer vaccination complications are under development but not yet licensed. In discussion it was emphasized that safety of newer vaccine candidates could be demonstrated in human trials but that efficacy is not. Members of the Committee stressed the need for the application of existing

[4] See the following web site for details of the WHO Prequalification Programme: http://apps.who.int/medicinedocs/documents/s14087e/s14087e.pdf (accessed 5 November 2009).

[5] Esposito JJ et al. Genome sequence diversity and clues to the evolution of variola (smallpox) virus. *Science* 2006, 313: 807.

immunological benchmarks (including antibodies and T-cell activation) in the comparison of different types of vaccine. Proposals were made for rationalizing the terminology of vaccines produced in different ways in order to convey information clearly to broader audiences.

4.6. Dr J. Huggins presented a comprehensive joint review of antiviral agents which have shown anti-variola virus activity, including immunobiological preparations. Three compounds (cidofovir, ST-246 and CMX001) that inhibit variola virus replication in vitro and in multiple surrogate animal models have obtained Investigational New Drug (IND) status from the US Food and Drug Administration (FDA). Intravenous cidofovir and oral ST-246 have demonstrated protection in the intravenous variola/primate model whereas CMX001 has not. As it is not possible to conduct human trials against an eradicated disease, demonstration of efficacy for the FDA must use the "animal rule", and the associated uncertainties render it difficult to provide firm estimates of timelines for drug approval. Similar uncertainties exist in other countries. The Institute of Medicine Committee was firm in its conclusions that the use of live variola virus was vital for the development and licensure of smallpox therapeutics.[6] The Advisory Committee recalled that capability to perform work with live variola virus must be maintained at least until two anti-variola drugs with different mechanisms of action have gained regulatory approval and could be used to combat an outbreak.

4.7. Dr P. Jahrling presented a joint review of animal models and pathogenesis, noting the broad availability of many orthopoxvirus models in rodents inter alia. Non-human primate models for monkeypox or variola infections can recapitulate some but not all features of human disease and it was argued that further research should be done after thorough evaluation of previously obtained data. Animal experiments have shown the efficacy of candidate vaccines and antiviral agents in several of these models. It is likely that no single combination of conditions will result in a model that would satisfy the criteria of some regulatory authorities. Refinements to the models have included exploring better routes of viral infection, application of technologies such as telemetry and imaging, and further use of biomarkers as triggers for early intervention. The experiments have shown a variety of responses but it is hard to extrapolate even between mice strains let alone to humans.

5. Updates on WHO-approved research proposals

5.1. Dr K. Karem described investigation into the potential usefulness of wild-caught prairie dogs (*Cynomys ludovicianus*) as a model for human smallpox. This system was chosen as a result of an outbreak of monkeypox in the USA, and subsequent infection modeling showing that infection of the animals with monkeypox virus mimicked the course of human smallpox. However, the animals infected with variola virus showed no signs of illness and were culture negative for virus at 14 days. Infected animals in the study seroconverted and some showed markers of protective immunity. Because of the lack of

[6] "The committee concludes that, for both scientific and regulatory reasons, the final developmental stages leading to licensure of smallpox therapeutics cannot occur without the use of live variola virus. … The most compelling reason for long-term retention of live variola virus stocks is their essential role in the identification and development of antiviral agents for use in anticipation of a large outbreak of smallpox" (Institute of Medicine. *Live Variola Virus: Considerations for Continuing Research*. Washington DC, The National Academies Press, 2009).

overt illness, the prairie dog was not considered to be a good animal model for variola virus infections.

5.2. Dr K. Karem further reported an update on the development of protein-based diagnostics, in particular the difference in sensitivity of an antigen-capture ELISA towards gamma-irradiated or live variola virus antigen. The difference was found to be attributable to gamma-irradiation, which most likely provoked the display of an epitope which was more reactive than in the live virus. Work will be proposed in order to continue investigation of protein-based diagnostics and the development of point-of-care assays that are simple to use, stable, robust and easy to interpret.

5.3. Dr I. Damon presented results on the development of less reactogenic third-generation vaccines through study of the neutralization capacity of serum following vaccination with MVA. Previous data on one MVA vaccine candidate had shown its ability to induce an anti-variola neutralization response (PRNT) in human volunteers, after two-dose inoculation, as high or in some cases higher than the first-generation Dryvax® vaccine. Recent preliminary studies suggest that volunteers vaccinated with another MVA vaccine candidate appear to mount an anti-variola neutralization response that is boosted on administration with Dryvax® six months after initial vaccination. Work is continuing to assess analytical methods and to repeat testing on some samples. The Committee noted that data comparing the neutralization of vaccinia virus and variola virus in parallel assays using virus stocks prepared in a similar manner were not yet finalized and available. Such data would be necessary to justify the need for live variola virus in neutralization assays.

5.4. Dr V. Olson reported on the collection of variola virus stocks held in the repository at the CDC: 451 isolates and specimens, with no withdrawals or additions in the past year. There have been 23 withdrawals from working stocks (stocks moved from the repository to the high-containment laboratory) for work on six WHO-approved protocols, including the regeneration of non-infectious material, particularly DNA samples, for running control diagnostic assays. The Committee was reminded of the real-time polymerase chain reaction assays established at CDC and which involve four different genomic regions. The specificity of these assays was 100% and the sensitivity was detection of five genome copies from purified virus. A kit for inactivating variola virus for DNA extraction was validated, with complete inactivation achieved rapidly.

5.5. Dr S. Shchelkunov reported data on the variola virus collection at the VECTOR centre in the Russian Federation. At present the collection holds 120 strains. The repository also contains variola virus DNA: 199 vials containing full-length variola virus genome DNAs from 39 different variola virus strains; 1446 vials, comprising 17 individual collections of amplicons with variola virus DNA fragments; and 3795 vials comprising 16 individual collections of recombinant plasmids with variola virus DNA fragments.

5.6. Dr Olson updated the Committee on work on potential therapeutic agents using live variola virus, in particular inhibitors of protein tyrosine kinases, which have been evaluated for use against human cancers. (Two of these inhibitors, imatinib (Gleevec) and dasatinib (Sprycel), have already been licensed for use in cancer treatment.) At least one has shown promise in animal models of orthopoxvirus infections. The WHO-approved research has extended earlier work and shown that these inhibitors prevent

actin-tail polymerization and release of variola and monkeypox viruses from infected cells.

5.7. Dr H. Meyer reported on potential reservoirs of, and diagnostics for, cowpox virus (a historical misnomer). The present rarity of cowpox virus infections in cows might be attributed to improved animal husbandry, but cowpox virus infections have been seen in a variety of other animals: rats, cats, foxes, and zoo animals including elephants, some of which seem to be dead-end hosts of the virus. Human infections through zoonotic transmission have been reported. Serosurveys show the presence of infections in rodents and it is believed that rodents are the reservoir. Many virus isolates have been examined and considerable sequence diversity of their haemagglutinin gene was detected. A diagnostic algorithm for orthopoxvirus infections and polymerase chain reaction methods for screening were shown to be effective and valuable tools.

5.8. Dr A. Nitsche reported on the epidemiology of cowpox virus infections in Germany, but cases have been reported in other European countries as well. Transmission to humans from rats has been well documented; one case was in a person who had been vaccinated against smallpox. It seems that awareness of cowpox virus infections in humans is increasing, as reflected in the number of cases, but it may also be that ecological changes and the growing popularity of rats as pets contribute to the increase. Dr. Nitsche's team had identified infections due to different strains in wild rats, pet rats and "feeder" rats (rats used as food for animals such as those in zoos). One company is exporting 400 000 rats a year into Germany. Some 60% of rats coming from one supplier were found to be positive for cowpox by polymerase chain reaction assays. Cowpox viruses exhibited different virulence in rats, a finding that could correlate with the different strains that co-circulate. It was noted that the cowpox virus infections in rats may be a promising model of orthopoxvirus pathogenesis.

5.9. Dr R. Lanier described the development of CMX001, a lipid-conjugated version of cidofovir, for treatment of smallpox. The lipid tail enables the prodrug to be taken up into cells where it is cleaved in contrast to "traditional" prodrugs which are cleaved in plasma, with the result that significantly more drug is available in the target cell. Compared with cidofovir, CMX001 has greater in vitro activity against double-stranded DNA viruses (for example, 270-fold better activity than cidofovir against variola virus), is orally bioavailable and well tolerated in Phase I trials, and has no nephrotoxicity. It is being investigated for use against variola virus infections, cytomegalovirus infections (in Phase II trials) and BK virus infection. Pharmacokinetic data support once-a-week dosing. Numerous animal studies have been done in which the drug showed its efficacy against orthopoxviruses. Higher oxidative metabolism of CMX001 in monkeys necessitates efficacy trials with live variola virus in this species for comparison with cidofovir and extrapolation of a human dose through the active antiviral cidofovir diphosphate. CMX001 has been used in one patient with complications following smallpox vaccination; drug resistance did not develop and its plasma concentrations were in the expected range. Despite clearance of the infection, no efficacy conclusions can be drawn because the patient was receiving multiple antiviral treatments.

5.10. Dr D. Hruby updated the Committee on the development of ST-246, confirming the drug's potency, lack of toxicity and specificity. It has proven effective in multiple animal studies and is orally bioavailable. It has been tested in Phase I clinical trials and is now in Phase II safety trials; Phase III trials are planned. Work is in hand on

commercial-scale validation lots, and ST-246 has been given IND approval and fast-track status. It does not interfere with immunization with either ACAM2000 or MVA vaccines in non-human primates.

5.11. Dr H. Yokote updated the Committee on attenuated smallpox vaccine LC16m8 (a third-generation vaccine), which is licensed in Japan (since 1975) and currently being stockpiled there as a precaution against bioterrorist attacks. The vaccine is simple to administer, in a single dose with a bifurcated needle. National capacity for vaccine production is 80 million doses a year. Since the report to the Committee last year, work has continued on comparing the safety profile of the vaccine with that of Dryvax® in immunocompromised macaques, with no evidence of adverse reactions using LC16m8. An ongoing post-marketing surveillance study of 267 subjects has shown that the vaccine is well-tolerated, with no serious vaccine-related adverse effects (including in allergic subjects), and with high levels of vaccine take and seroconversion.

5.12. Dr Piffaretti presented a review of third-generation vaccines currently being examined in clinical studies, particularly MVA and LC16m8, in order to stimulate discussion and obtain advice that would guide WHO in its decision to acquire a stockpile of such vaccines. Major differences in these vaccines were noted. LC16m8 is replication-competent in humans and induces a take after the traditional scarification or puncture procedure with a bifurcated needle. It has been shown to be safe in initial studies, but more data are needed. MVA is replication-defective in humans and must be inoculated intradermally or intramuscularly at higher doses than LC16m8. Discussions stressed the importance of these two third-generation vaccines, which so far have demonstrated fewer complications than first- and second-generation vaccines in humans and which were thus more appropriate for use in special populations at risk of severe adverse events typically associated with first- and second-generation vaccines. It was suggested that for pre-event vaccination MVA might be preferred at the moment because of the existing large body of data on its safety but in an outbreak situation the use of both LC16m8 and MVA could be considered. While these third-generation vaccines are being examined, it should be recalled that the first-generation vaccine was very effective, being instrumental to the interruption of transmission of variola virus.

5.13. Dr M. Seghers presented a review of a study on the risks and benefits of vaccinating with smallpox vaccine health-care workers (HCW) exposed to Monkeypox. The topic was prompted by the ongoing circulation of Monkeypox virus in the Congo Basin and the outbreak of Monkeypox in the USA in 2003. Despite some anecdotal evidence, the study did not confirm evidence from the literature of HCW affected by Monkeypox in Africa. General recommendations were to follow standard infection control precautions (including personal protective equipment). During its discussion the Member of the Advisory Committee emphasized that vaccination of health-care workers and laboratory technicians exposed to Monkeypox virus might be considered because of the risk associated with exposure to Monkeypox virus. Issues relating to policies in areas where HIV infection was endemic should be explored. Other questions remained, in particular which vaccine to use and whether laboratory workers and animal care-givers should be vaccinated. The data from the US epidemic should not necessarily be taken as the model because the strain involved was less pathogenic, and apparently less transmissible from person to person, than the strain(s) circulating in the Congo Basin.

5.14. Ms M. Morsia-Villemin described the issues relating to the access and preservation of the extensive archives of the Smallpox Eradication Programme. These archives cover the period 1948-1987 and include not just paper documents (some 720 000) but images, photographs, tape recordings and old electronic files. Their physical state is deteriorating, and access for researchers is limited. A programme is under way to convert all the materials into a digital format which will allow full text searching, using optical character recognition as well as conversion into PDF files and other techniques. The Committee warmly welcomed this approach, and was informed that a similar project had captured comparable material collected by the CDC.[7]

5.15. Dr J.-C. Piffaretti presented an update on the proposal made last year for a smallpox laboratory diagnostic network whose purpose was to provide a mechanism for WHO to be informed of suspicious and true smallpox events and to ensure that false alarms were eliminated. The network would comprise the two existing WHO Collaborating Centres (CDC and VECTOR) and regional laboratories (the number of which remains to be determined, but possibly one per WHO Region). For the designation of the regional laboratories, an algorithm for processing suspicious samples and the required, stringent criteria were outlined. In discussion, the Committee heard that Member States with good existing systems and where mechanisms were in place would be included in the proposed network. The concept and approach were analogous to those for the laboratory response network in the USA. In some WHO regions transport of samples would be a problem (including air-transport regulations as well as logistics) and the location of a regional laboratory might not be optimal in terms of proximity to the problem, and a key question posed was how to transport a specimen that needs diagnosis and confirmation rapidly and securely to a reference laboratory. Suggestions were made to integrate the proposal into broader initiatives, for instance those related to the International Health Regulations (2005) or WHO's programmes on laboratory capacity building and networking. The Committee recommended formation of a subcommittee that included at least one member from both WHO Collaborating Centres in order to set up a process to identify the appropriate local and regional laboratories for initial diagnosis of suspect cases of smallpox, draft standard operating procedures, and design quality control and assurance mechanisms.

[7] http://www.globalhealthchronicles.org/

Annex 1: Agenda

11th Meeting of the WHO Advisory Committee on Variola Virus Research, from 4 to 5 November 2009 International Conference Center, Geneva (CICG) Switzerland

Agenda

4th November 2009

9:00 - 9:15	Opening – Dr K. Fukuda, Special Adviser to the Director-General on Pandemic Influenza, And on behalf of Assistant Director-General for Health Security and Environment
	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. Drillien
9:45 – 10:00	Summary of IOM Smallpox Report – D. Ulaeto
10:00 – 10:15	Review Paper: The current state of the variola virus stocks and repositories – I. Damon, E. Stavskiy
10:15 – 10:30	Discussion
10:30 – 11:00	**Tea/Coffee Break**
11:00 – 10:15	Review Paper: Laboratory Diagnostic of Smallpox (variola virus) – I. Damon, H. Meyer, S. Shchelkunov
11:15 – 11:30	Discussion
11:30 – 11:45	Review Paper: Variola Genomics – G. McFadden, S. Shchelkunov
11:45 – 12:00	Discussion
12:00 – 13:00	**Lunch**
13:00 – 13:15	Review Paper: Vaccines – A. Alcami, B. Moss
13:15 – 13:30	Discussion
13:30 – 13:45	Review Paper: Therapeutic Agents – J. Huggins, N. Tikunova
13:45 – 14:00	Discussion

14:00 – 14:15	Review Paper: Animal models and pathogenesis – P. Jahrling, A. Osterhaus, E. Ryabchikova
14:15 – 14:30	Discussion
14:30 – 14:45	Summary on review papers and discussion – R. Drillien/G.L. Smith
14:45 – 15:00	Determination of whether Variola infection of *Cynomys ludivicianus* is a suitable animal model for human smallpox – K. Karem
15:00 – 15:15	Protein based diagnostic development – K. Karem
15:15 – 15:30	Report on support for development of second and third generation smallpox vaccines – I. Damon
15:30 – 16:00	**Tea/Coffee Break**
16:00 – 16:15	2009 report on the variola collection of the WHO Collaborating Center Repository in Atlanta, USA – V. Olson
16:15 – 16:30	Report on the use of live Variola virus to evaluate therapeutic modalities: *in vitro* studies – V. Olson
16:30 – 16:45	Cowpoxvirus: reservoir and diagnostics – H. Meyer
16:45 – 17:00	Epidemic of cowpox infections in Germany transmitted from rats – A. Nitsche
17:00 – 17:15	Update on hexadecyloxypropyl cidofovir (CMX001) drug development – R. Lanier
17:15 – 17:30	Update on ST-246 drug development – D. Hruby
17:30 – 17:45	Update on attenuated smallpox vaccine LC16m8 – H. Yokote
17:45 – 18:00	Discussion on 3rd Generation Vaccines – J.-C. Piffaretti
18:15 – 18:30	Review of research proposals: designation of secondees for the scientific subcommittee – D. Lavanchy
18:30 – 19:30	***Social event***

DAY 1 CLOSES

5th November 2009

9:00 – 9:15	Vaccination of health-care workers – M. Seghers
9:15 – 9:30	Discussion

9:30 – 9:45	Smallpox archives, status update – M. Morsia-Villemin
9:45 – 10:00	Update on Smallpox Laboratory Diagnostic Network – J.-C. Piffaretti
10:00 – 10:15	Discussion
10:15 – 10:45	**Tea/Coffee Break**
10:45 – 11:00	Miscellaneous
11:00 – 12:00	General discussion and preparation of draft recommendations
12:00 – 13:30	**Lunch**
13:30 – 15:00	Final discussion of draft recommendations

ACVVR MEETING CLOSES

15:00 – 15:30	**Tea/Coffee Break**

Monkeypox

15:30 – 16:00	Update on human monkeypox epidemiology in DRC – A.W. Rimoin
16:00 – 16:30	Update on the Kole monkeypox project in DRC – J. Huggins
16:30 – 17:00	Genome analysis and genetic diversity between monkeypox virus strains – I. Damon
17:00 – 17:30	General discussion and outlook – P. Formenty

MEETING CLOSES

Annex 2. List of participants

11th Meeting of the WHO Advisory Committee on Variola Virus Research, from 4 to 5 November 2009 International Conference Center, Geneva (CICG) Switzerland

PARTICIPANTS

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