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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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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