World Health Organization

SIXTY WORLD HEALTH ASSEMBLY **A60/40**
Provisional agenda item 12.2 **29 March 2007**

Smallpox eradication: destruction of variola virus stocks

Eighth meeting of the WHO Advisory Committee on Variola Virus Research

Report by the Secretariat

1. The present document reports on the meeting of the WHO Advisory Committee on Variola Virus Research held since discussion at the Fifty-ninth World Health Assembly on destruction of variola virus stocks.[1]

2. The Advisory Committee on Variola Virus Research was established pursuant to resolution WHA52.10, which authorized temporary retention of the existing stocks of variola virus at the two current locations[2] up to, but not later than, 2002 and subject to annual review by the Health Assembly. The resolution also requested the Director-General to appoint a group of experts to establish what research, if any, must be carried out in order to reach consensus on the timing for the destruction of virus stocks.

3. In resolution WHA55.15, the Health Assembly authorized the further, temporary, retention of the existing stocks of live virus on the understanding that all approved research would remain outcome-oriented and time-limited, and its accomplishments and outcomes would be periodically reviewed. The resolution requested the Director-General to continue the work of the Advisory Committee and to report annually to the Health Assembly, through the Executive Board, on progress in the research programme and relevant issues. At its eighth meeting (Geneva, 16 and 17 November 2006), the Committee reviewed progress in research using live variola virus since its previous meeting in 2005.

4. **Virus strains in the two repositories.** The Committee reviewed data on the variola virus strains and primary isolates held in the two collections and noted no changes. As recommended in previous meetings, these collections had been subject to an annual inventory using a unifying system. The Committee was satisfied that materials in the two collections corresponded to the inventories and were being maintained with appropriate safeguards in place.

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[1] See document WHA59/2006/REC/3, summary records of Committee A, seventh and eleventh meetings.

[2] Russian State Centre on Virology and Biotechnology, Koltsovo, Novosibirsk Region, Russian Federation and the Centers for Disease Control and Prevention, Atlanta, Georgia, United States of America.

5. Sequence analysis of variola virus DNA. This issue was recognized as contentious because the Committee had previously recommended that no further full-length genomic sequences were needed. Questions were raised about the lack of complete coverage in the collections of viruses representing the full range of virulence and geographical diversity. The Committee recommended that a review of the literature on known variola virus strains should be undertaken in order to determine whether any unusual epidemiological or clinical characteristics have been documented that would merit further investigation. Pending the outcome of that review, it was considered that the DNA information currently available was sufficient to fulfil the needs of protecting public health and, therefore, that no new work on live viruses was needed in order to generate additional information. The matter may be reconsidered if the outcome of the literature review indicates otherwise.

6. Diagnostic assays. The Committee noted progress in the development of a solid-membrane assay suitable for use in the field which could detect the presence of orthopoxviruses or varicella virus in individuals presenting with symptoms consistent with smallpox infection. Diagnostic results could be obtained within two to four hours. These preliminary results will require validation and confirmation. The Committee recommended that, if validated, these tests should be made widely available in as many countries as possible. It also recommended that validated detection kits should be distributed to designated reference laboratories, and that information on procedures for shipping clinical samples from suspected cases to an appropriate reference laboratory should be widely disseminated. The Committee also asked the Secretariat to establish an informal network dedicated to the diagnosis of orthopoxviruses, although it noted that a single diagnostic strategy could not be developed as much would depend on national capacity and expertise. The Committee also reviewed preliminary data on a diagnostic assay based on protein-array technology, and agreed that additional studies will be needed to evaluate its robustness, stability, sensitivity and specificity.

7. Vaccines. The Committee was reminded of the need for a safer vaccine against smallpox and an update was provided on some of the more promising initiatives in this area. Current understanding of the protein targets of the immune response following smallpox vaccination, however, is insufficient for the evaluation of new candidate vaccines. The role of different viral proteins and their relation to the generation of a protective immune response is the subject of further study. A comparison of neutralizing antibodies induced against variola and vaccinia viruses is under way.

8. Animal models. The Committee noted the further refinements in the primate model of human smallpox. The monkeypox virus infection model in non-human primates could produce useful correlates with variola virus infection in humans. The Committee was also presented with data from recent experiments in the primate model in which disease was successfully induced, with features similar to that of lesional or common smallpox and haemorrhagic smallpox in humans. These results represent significant progress towards a closer approximation to a human disease model. These studies furthered the understanding of different phases in the progression of the disease and were considered useful for the assessment of the efficacy of antiviral drugs. The Committee agreed that further improvements in the animal model of smallpox were desirable in order to continue assessment of antiviral drug candidates, and to ensure that regulatory requirements for licensing in some countries are met.

9. Antiviral drugs. The Committee reviewed the data available on the development of cidofovir and ST-246, a new candidate antiviral drug. Cidofovir has a proven efficacy in orthopoxvirus infections and protocols have been submitted to the Food and Drug Administration in the United States of America for consideration under the special protocol assessment provision. ST-246 is 8000 times more potent than cidofovir and can be administered orally. It is effective against all orthopoxviruses tested. Studies for gaining regulatory approval of the drug are now in progress. ST-246 is now regarded as highly promising, and may have potential to become the drug of choice,

but cidofovir should still be considered useful, particularly as the human safety of this drug has already been established. The Committee noted that considerable therapeutic benefit was obtained with ST-246 and it was agreed that further work to define the clinical efficacy of this compound was required.

10. Distribution of variola virus DNA fragments and transfer of such material to third parties. Distribution of variola virus DNA fragments has been authorized in the past for specific human health-related research according to rules established by WHO with the advice of the Ad Hoc Committee on Orthopoxvirus Infections, and, more recently, the Advisory Committee. The transfer of such material has been conditional on the presentation of annual reports describing its use to WHO. The Committee noted that reporting has been incomplete and it urged the Secretariat to request reports from laboratories. It was stressed that DNA samples must be destroyed if the reports indicated they were not being used for the work intended.

11. The Committee was requested to state its opinion on the acceptability of the transfer of variola virus DNA samples from laboratories authorized to work with this material to third parties. Recent technological developments have increased the interest in research into variola viruses and concerns have been raised that WHO's restrictions on the manipulation of variola virus genes may not be known by the wider scientific community. It was recommended that transfers to third parties take place only on the condition that approval is sought from, and granted by, the Secretariat. The Committee decided that a technical subcommittee should review the existing rules, propose revisions and report back to the Committee at its next meeting. The Committee also recommended that the revised rules should then be distributed to all WHO country offices and regulatory bodies, and published on the WHO web site in order to raise general awareness of this issue.

12. **New or updated proposals submitted to WHO.** In prior meetings the Committee recommended that all research that used live variola virus in the two Collaborating Centres must have a clear and essential public-health benefit and be time-limited. A scientific subcommittee was therefore established to review research proposals. Since the last meeting of the Committee, seven projects had been approved and five rejected. Decisions on a further seven projects were still pending the outcome of ongoing review by all members of the scientific subcommittee. It was noted that, although all the proposals submitted were found to be scientifically sound, those rejected did not meet the criteria required to have access to live variola viruses.

13. Suggestions were also made for improving the process of reviewing proposals for research on live variola virus. It was agreed that the decision-making process needed to be streamlined and that the response should be sent to the authors within two months of the original submission. In the event of a rejection, a process was defined involving re-examination of proposals by the whole Advisory Committee.

14. Lastly, it was agreed that the membership of the scientific subcommittee should be reviewed and that up to one third of its membership should be replaced on an annual basis. In order to avoid potential conflicts of interest, the Committee decided to maintain the policy of excluding the participation of staff from the collaborating centres in the scientific subcommittee.

15. The above report was discussed by the Executive Board at its 120th session in January 2007.[1]

ACTION BY THE HEALTH ASSEMBLY

16. The Health Assembly is invited to note the above report.

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[1] See document EB119/2006–EB120/2007/REC/2, summary record of the eleventh meeting of the 120th session of the Board, section 2.