World Health Organization

SIXTY-FIRST WORLD HEALTH ASSEMBLY **A61/6**
Provisional agenda item 11.3 **14 April 2008**

Smallpox eradication: destruction of variola virus stocks

Report by the Secretariat

1. This document reports on the ninth meeting of the WHO Advisory Committee on Variola Virus Research (Geneva, 28 and 29 November 2007) and on the work of the Secretariat. The Advisory Committee was established pursuant to resolution WHA52.10, in which the Health Assembly authorized temporary retention of the remaining stocks of live variola virus, and requested the Director-General to appoint a group of experts to determine what research, if any, must be carried out in order to reach consensus on the timing for the destruction of these virus stocks. 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. It also requested the Director-General to report annually to the Health Assembly, through the Executive Board, on progress in the research programme and relevant issues. In resolution WHA60.1, the Health Assembly requested the Director-General to undertake a major review in 2010 of the results of the research undertaken and currently under way, so that the Sixty-fourth World Health Assembly may reach global consensus on the timing of the destruction of existing variola virus stocks.

2. **Update on research proposals submitted to WHO.** The Advisory Committee received a summary of the research proposals approved (12 work programmes) and rejected (12) by its scientific subcommittee. Many of the approved projects are coming to their end, on schedule, and final reports should be submitted. Recently received new proposals will be evaluated according to the revised procedure agreed upon during the Committee's eighth meeting in 2006[1] and requiring a rotation of the membership of the scientific subcommittee. The Committee accepted the new membership of the subcommittee.

3. **Virus strains in the two repositories.**[2] 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] Document EB120/39.

[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.

4. **Sequence analysis of variola virus DNA.** As previously recommended by the Committee, no further sequencing of genomic DNA was undertaken, with the exception of the sequencing of an Asian strain in the Russian collection, which is currently under way in the Russian collaborating centre in order to complete the coverage of geographical diversity of the viruses.

5. **Clinical manifestations of smallpox.** In response to the Committee's previous recommendation that a review of the archives be undertaken to determine whether there is any correlation between particular variola virus isolates and the severity of clinical manifestations of smallpox, the Committee was presented with the results of an analysis of the records archived at WHO. Most of these records contain little or no clinical information. This investigation therefore yielded no information that would allow linking particular virus isolates to disease characteristics.

6. **Animal models using live variola virus.** The Committee noted that many of the objectives of the work to refine the primate model of human smallpox for testing antiviral compounds had now been achieved, but further work may still be needed to make the model more suitable for testing such compounds in order to obtain licensure.

7. **Antiviral drugs.** The Committee noted recent progress on the development of the antiviral drug, ST-246, which suppresses orthopoxvirus growth in vitro, is active in treating a variety of orthopoxvirus infections in animal models, and appears to be safe and well tolerated in those models. Data on efficacy in different animal models have been submitted to the Food and Drug Administration in the United States of America. The Committee was also informed that these preliminary results with ST-246 were sufficiently positive that small amounts of the drug were being stockpiled by the company producing it for emergency, compassionate use. Work is in progress to determine if ST-246 can be used in immunocompromised or pregnant individuals.

8. **Vaccines.** The Committee reviewed promising new approaches. A new smallpox vaccine (ACAM 2000) has been licensed for use in one Member State. Work on two third-generation vaccines (MVA and LC16m8) showed that these are safe and less reactogenic, and preliminary data suggest that successful individual vaccination and level of induction of neutralizing antibodies were comparable to those for first- and second-generation vaccines. Further studies on both vaccines are in progress. The Committee discussed regulatory issues concerning requirements for licensing third-generation vaccines, highlighting the absence of a satisfactory animal model for testing smallpox vaccines and the lack of knowledge of the correlates of protection against human smallpox. It appeared, however, that an animal model using live variola virus will not be mandatory for licensing a third-generation vaccine by at least two regulatory agencies.

9. **Use of antiviral immunoglobulin, cidofovir and ST-246 in the treatment of eczema vaccinatum.** Treatment of a case of life-threatening eczema vaccinatum was reported. The Committee noted that the use of ST-246 appeared to have been particularly beneficial and was followed by the recovery of the patient. ST-246 should therefore be considered as an early treatment option if safety and efficacy in humans are confirmed by further studies.

10. **Review of research work done by laboratories that have obtained variola virus DNA with WHO's approval.** As part of its obligation to oversee research activities using portions of variola virus DNA, the Secretariat presented some preliminary data from a survey of laboratories known to be engaged in this research. The subject laboratories were identified through WHO's records of approved requests for variola virus DNA fragments, and records of the Centers for Disease Control and Prevention of distributions of variola virus fragments, and publications related to variola DNA fragments since 1994. Although one Committee member expressed concern about the methodology used in collecting the preliminary data, the Committee welcomed this effort. It considered that WHO

should continue to have access to up-to-date information on the use and distributions 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 recommended that the Secretariat should continue its efforts to increase awareness of the regulations and guidelines governing the use and distribution of variola virus DNA.

11. **Transfer of variola virus DNA.** The Committee recommended that the wording of the current recommendations and guidelines about the transfer of variola virus DNA 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. A major concern was the transfer of DNA fragments from laboratories whose projects have been approved by WHO to third parties. The Committee agreed that such transfer requires authorization by WHO and should be controlled, for example, through appropriate material transfer agreements between the distributing and receiving laboratories, with a copy sent to WHO.

12. **Measures to promote wide and equitable access to research outcomes.** The Committee reviewed all the topics mentioned in the Health Assembly's request to the Director-General in resolution WHA60.1 to report on "measures that promote in Member States the widest and most equitable access possible to the outcomes of the research, including antiviral agents, vaccines, and diagnostic tools". Preliminary discussions were held about the availability of antiviral drugs and newer vaccines, but currently these reagents are not yet sufficiently advanced to plan large-scale applications; the Committee will reconsider these items in the future as research progresses. In regard to access to first- and second-generation vaccines, WHO continues to work to enlarge the vaccine supply in its global vaccine bank, and is receiving supplies of second-generation vaccine for the vaccine stockpile held in Switzerland. Should the newer vaccines prove to be both safe and immunogenic, WHO should accept them in the vaccine bank, and Member States producing or purchasing such vaccines should be encouraged to contribute to the stockpile. The Secretariat reported on initial steps taken to set up an informal network of laboratories for the diagnosis of orthopox infections, including smallpox. The plan is to have at least one laboratory, and preferably several, in each WHO region capable of applying orthopox diagnostics in a reliable and efficient manner, including preliminary diagnosis of suspected smallpox using molecular methods on inactivated clinical material. The result would be more rapid access to results on samples from patients and the saving of shipping costs. A tentative list of participating laboratories was presented, but the Committee decided that more consultation was needed to determine which laboratories are interested and qualified to participate. Such a network would require a system to evaluate and maintain reliability of results, and the Secretariat is working with WHO collaborating centres to determine the necessary support.

13. The Executive Board noted an earlier version of the above report at its 122nd session in January 2008.[1]

[1] See document EB122/2008/REC/2, summary record of the tenth meeting, section 2.

FOLLOW-UP BY THE SECRETARIAT

Legal status of variola virus stocks held at the two repositories

14. The Health Assembly in resolution WHA33.4 endorsed the recommendations of the Global Commission for the Certification of Smallpox Eradication, including the recommendation that no more than four WHO collaborating centres should be approved as suitable to hold, and handle, stocks of variola virus. The number of collaborating centres was reduced to two in 1983. In light of the process followed by institutions around the world to transfer their stocks of virus to the two designated WHO collaborating centres, and on the basis of what WHO has retained in its archives from the period in question, it appears that transfers effected at the time were not necessarily performed with a clear specification of the legal basis on which virus strains were transferred and would be held by the recipient repositories.

15. The Health Assembly in resolution WHA60.1 requested the Director-General to submit to the Sixty-first World Health Assembly a report on the legal status of the variola virus strains held at the two repositories with respect to their ownership. In view of the lack of sufficient information to produce that report, the Secretariat requested the assistance of the 10 Member States with declared virus stocks in 1977, asking, in particular, for any information or records that could clarify the legal status of virus stocks transferred or held by them, as the case may be, pursuant to the relevant Health Assembly resolutions. As of 10 April 2008, replies had been received from seven countries.

16. The legal status of the variola virus strains in question is related to the factual as well as the documentary and legal circumstances surrounding their transfer. However, the available record, including the responses to the Secretariat's request, is insufficient to provide a complete analysis of these circumstances. On the basis of the sparse records available in WHO and the replies received, some Member States transferred their remaining virus stocks to the WHO collaborating centres on the understanding that the ownership rights of the transferring institutions were terminated. On the other hand, another Member State has indicated that it transferred stocks, while regarding itself as retaining ownership rights. Other Member States reportedly did not address ownership rights in the documentation accompanying their transferred samples. Accordingly, on the limited documentary basis available, there appear to be uncertain, as well as variable, ownership scenarios for the stocks in question at the two repositories.

Research projects

17. The Secretariat has prepared a list of research projects that have been permitted by WHO for the