



WORLD HEALTH ORGANIZATION

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Smallpox eradication: destruction of variola virus stocks

Report by the Secretariat

1. In May 1999 the Health Assembly by resolution WHA52.10 decided to authorize temporary retention up to, but not later than, 2002 of the existing stocks of variola virus at the current locations,¹ for the purpose of further international research. The Assembly requested the Director-General to appoint a new group of experts to establish what research, if any, must be carried out in order to obtain consensus on the timing for the destruction of the existing variola virus stocks.
2. In accordance with this resolution, a new group of experts, designated the WHO Advisory Committee on Variola Virus Research, was appointed, composed of 16 members from different countries, with representatives from all WHO regions. At its first meeting (Geneva, 6 to 9 December 1999), attended also by 10 advisers representing fundamental and applied research and regulatory agencies, the Committee first focused on the need for further research on the variola virus in order to obtain consensus on the date of destruction of virus stocks. In the Committee's view further limited research on variola virus could be justified, but under no circumstances should this go beyond the end of 2002. The Committee then agreed on priority areas for, and nature of, future research.
3. **DNA sequence information.** It was argued that the sequence information currently available was insufficient to provide consensus information across the full range of virus strains available. The Committee concluded that full-length genome sequences from additional variola major and minor strains, particularly Congo 70 and Somalia 77, should be determined and that additional clone libraries from selected strains should be prepared. Scientists wishing to undertake those studies should establish a work programme that did not exceed the end of 2002.
4. **Diagnostic tests.** The need for novel diagnostic tests for variola virus in case smallpox should reappear was discussed. New types of diagnostic and detection procedures for infectious agents had been developed and some had already been incorporated into state-of-the-art equipment. Those procedures and devices were able to detect infections early and with great sensitivity, but they needed further validation for use with variola virus under simulated field conditions, which would require access to the live stocks. The Committee recommended completion of the validation of detection/diagnostic tests and equipment using live variola virus if necessary. The sensitivity of the procedures should be confirmed and protocols developed for use in early diagnosis with readily available clinical specimens.

¹ WHO collaborating centre for smallpox and other poxvirus infections, Centers for Disease Control and Prevention, Atlanta, Georgia, United States of America; WHO collaborating centre for orthopoxvirus diagnosis, State Research Centre of Virology and Biotechnology, Koltsovo, Novosibirsk Region, Russian Federation.

5. **Antiviral drugs.** Several Committee members felt that antiviral drugs were needed to treat clinical smallpox disease. Some lead compounds had already been identified, but more work was needed to provide better formulations. To gain approval of regulatory authorities in different countries, nonclinical efficacy data from animal model studies and infected cell cultures might be needed for those drugs to be used in the case of smallpox infections. Other members argued that an antiviral drug would also be useful for the treatment of the rare complications of vaccination with vaccinia virus, which is used as vaccine against smallpox. The Committee therefore recommended encouraging work that would lead to the development of drugs which could treat progressive vaccinal disease, and to the completion of the drug development programme on existing lead compounds and on all work requiring access to live virus, with a view to obtaining approval by 2002. It was recommended that benchmarks should be devised against which progress could be monitored by independent observers.

6. **Hyperimmune globulin and neutralizing antibodies.** The Committee noted that supplies of hyperimmune globulin and neutralizing antibodies to the two infectious forms of variola virus were extremely limited. These preparations may have potential therapeutic or prophylactic use. Relatively few monoclonal antibodies were available and access to more could provide additional material for use in diagnosis. Access to live virus stocks would be needed during the initial stages of monoclonal antibody production or if, for example, phage display systems were to be developed. The Committee recommended the establishment of a time-limited programme for production of monoclonal antibodies.

7. **Vaccines.** The arguments for further work on vaccine development were based on the view that a safer, but similarly efficacious, vaccine was needed. It was noted that new vaccine preparations derived from tissue culture are required as the old method of production (animal skin scarification) was no longer acceptable in some countries. Moreover, approval of new or novel smallpox vaccines (replication-deficient, recombinant, etc.) by regulatory authorities in different countries would be needed which would require validation data using live variola virus. It was agreed that production of a tissue-culture-derived vaccine based on a validated vaccinia strain was the most appropriate way forward, but that this should not preclude development of a secondary vaccine that could be deployed in populations at risk. The view was expressed that although research on these other vaccines should not be discouraged, it should be recognized that they may not be licensable by regulatory authorities in different countries. Further work on vaccine development should be encouraged, but this should not be dependent on gaining access to live variola virus stocks. The new tissue-culture-derived vaccines using vaccinia virus strains of well-documented efficacy are considered less likely to require validation with live virus for regulatory approval.

8. **Animal models.** It was argued that regulatory requirements for the introduction of new drugs would require nonclinical efficacy data in animals that were infected with variola virus. Some work on the development of these, as opposed to surrogate models (e.g. ectromelia virus in mice, monkeypox virus in monkeys) was therefore needed. Some work was already planned to assess the utility of cynomolgus macaques for this purpose. It was noted that other animals (suckling mice, transgenic mice) might be suitable hosts to support virus replication. Work to develop an acceptable animal model that could be infected with variola virus was therefore justified. The availability of a validated animal model would also be useful to evaluate the sensitivity and specificity of diagnostic tests.

9. Most participants accepted the arguments behind the need for research in this area but noted that smallpox virus research had been ongoing for decades and a suitable animal model had yet to be identified. It was doubtful whether any model that might be developed would produce data that could be directly correlated with human infections. The Committee recommended that limited exploration be undertaken of the susceptibility of nonhuman primates and other species to infection with defined variola viruses whose genomic sequences are likely to be determined. A time-limited work plan

defining species, variola virus strain, dose and inoculation route should be developed. Successful development of an animal model should be completed as soon as possible to facilitate evaluation of antiviral drugs, vaccines and diagnostic tests.

10. Some members argued that it was essential to continue to support basic research using live variola virus to further understanding of all aspects of the pathobiology of this human pathogen. Others maintained that this would have a low priority and that, in order to conduct meaningful research, access to a suitable animal model would be needed, which could not be guaranteed. It was suggested that this aspect of a potential research programme should be dropped from further consideration as much information could be derived by using other orthopoxviruses. However, the Committee noted that further research on variola viruses was being proposed and while this research was being done, work of a more fundamental nature might proceed in parallel, providing it did not entail open-ended research. Work plans for time-limited work of a fundamental nature with benchmarks and defined end-points should be established.

11. **Oversight of research.** Lastly, it was recommended that a WHO scientific subcommittee be established for the purpose of overseeing future research on variola virus, with members of this subcommittee to be drawn from the Advisory Committee on Variola Virus Research. It was further recommended that the subcommittee should comprise five members, including one member from each of the two WHO collaborating centres currently holding variola virus, where all of the approved work would be performed.

12. As stipulated by resolution WHA52.10, financing of research will be left to WHO Member States or other national or international bodies which may wish to support such work. The scientific subcommittee will receive and evaluate research proposals before they are submitted to funding agencies to ensure that the proposed work fits the research priorities and time-frame defined by the Advisory Committee. Research proposals should to be processed within four weeks of receipt.

13. Scientists wishing to perform research on variola virus will need permission from the WHO collaborating centres in Atlanta or Koltsovo in order to perform the work in those institutions.

ACTION BY THE EXECUTIVE BOARD

14. The Board is invited to note the report.

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