



WORLD HEALTH ORGANIZATION

FIFTY-NINTH WORLD HEALTH ASSEMBLY
Provisional agenda item 11.5

A59/10
18 May 2006

Smallpox eradication: destruction of variola virus stocks

Report by the Secretariat

1. The WHO Advisory Committee on Variola Virus Research was established pursuant to resolution WHA52.10, which authorized temporary retention of existing stocks of variola virus at the two current locations¹ 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 of destruction of variola virus stocks.
2. In resolution WHA55.15, the Health Assembly authorized the further temporary retention of the existing stocks of live virus, for the purpose of enabling further international research, 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.
3. This document provides a report of the Advisory Committee's seventh meeting (Geneva, 10 and 11 November 2005), which reviewed progress in research with live variola virus since the previous meeting, in 2004.

SEVENTH MEETING OF THE WHO ADVISORY COMMITTEE ON VARIOLA VIRUS RESEARCH

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 change in the content of the inventories since the previous year. These materials had been inventoried, as recommended at previous meetings, 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. It reviewed procedures for responding to requests for the distribution of short DNA fragments of the virus, needed for work on the development of diagnostic tests, and was informed of some difficulties in obtaining these fragments. The Committee agreed that a solution should be found.

¹ Russian State Research Centre of Virology and Biotechnology, Koltsovo, Novosibirsk Region, Russian Federation, and the Centers for Disease Control and Prevention, Atlanta, Georgia, United States of America.

5. Work to assess the viability of strains held in the Russian collection was continuing. DNA from the collection was being preserved; a reliable method for long-term conservation had been devised and applied.

6. The Committee noted that not all viral isolates held in the two collections are viable, and that hybrid viruses in the United States collection are still being preserved. The Committee found no scientific justification for performing further research on these viruses.

7. **Sequence analysis of variola virus DNA.** Work on the construction of phylogenetic trees of variola viruses, conducted since the Committee's previous meeting, had further broadened understanding of their evolutionary history. The Committee agreed that sufficient sequence information on the virus was now available; no further research requiring access to live variola virus was considered essential for this purpose.

8. **Animal models.** The Committee noted further work on the primate model of human smallpox, which had been undertaken to facilitate the development of antiviral drugs and to meet regulatory requirements, in some countries, for their licensing. Recent experiments in primates, using different doses of virus, had induced disease with features similar to that of lesional, or common, smallpox and haemorrhagic smallpox in humans. These studies furthered understanding of specific organ and tissue sites of virus replication at different phases of disease progression and were thus considered useful in studies designed to assess the efficacy of antiviral drugs.

9. The Committee agreed on the desirability of further improvements in the animal model of smallpox, but asked for precise proposals on research strategies for achieving this objective. Clarification was requested on the implications of the regulatory requirements for the licensing of new medicines in the United States of America, which make an exception for diseases such as smallpox, where clinical trials of such drugs in human volunteers are not possible, and allow approval on the basis of the results of animal studies only. These requirements could help to determine how closely disease in an animal model of smallpox needs to resemble clinical disease in humans. One research strategy for meeting regulatory requirements quickly and obviating the need for further work using live variola virus was to determine whether infections of monkeys with monkeypox virus might substitute for the animal model for smallpox.

10. **Diagnostic assays.** The Committee noted great progress in the development of sensitive and reliable diagnostic tests using real-time polymerase chain reaction methods. Data presented to the Committee showed that recently developed tests for the diagnosis of variola virus infection can produce definitive results within two to four hours of submission of a clinical specimen. Specificity of the tests was greater than 99%. In view of this accomplishment, the Committee recommended that the tests should be made widely available and adapted for field use in as many countries as possible, because an adequate response to a possible smallpox outbreak would require global case surveillance. Proposed strategies for doing this included the distribution of validated detection kits to designated clinical centres and reference laboratories, and the broad provision of information on how to ship clinical samples that may contain variola virus to an appropriate reference laboratory.

11. The Committee further noted that reference laboratories might need more than one diagnostic assay to distinguish reliably infection with variola virus from infection with other orthopoxviruses. Reliable differential diagnosis was considered especially important in view of the serious consequences of a misdiagnosis of smallpox. In this regard, the Committee noted that several diagnostic tests had been developed in various laboratories but required validation. The Committee reviewed data from studies of an IgM-based enzyme-linked immunosorbent assay for the diagnosis of monkeypox as a further aid to differential diagnosis. Results showed that, when used for the diagnosis

of acute monkeypox infection, test specificity and sensitivity approached 95%. As the test would be most useful in Africa, where most human outbreaks of monkeypox occur, the Committee recommended that validated reagents and protocols be made more widely available, particularly in Africa.

12. The Committee concluded that the number of detection and diagnostic systems for variola virus now available was adequate. Although full agreement was not reached, most members of the Committee held the view that no additional research involving the use of live variola virus or hybrid viruses was required for this purpose.

13. **Antiviral drugs.** Cidofovir and its analogues continue to be the most promising antiviral drugs either already licensed or in advanced experimental studies. The Committee reviewed data on a cidofovir analogue that could be administered orally. Another candidate antiviral drug, unrelated to cidofovir, showed far greater potency in some early tests, but has not yet been studied in sufficient detail to allow firm conclusions about its utility compared with cidofovir.

14. The Committee noted that requirements for regulatory approval of antiviral agents in the United States of America include demonstration of direct activity against variola virus. Further work to gain regulatory approval of candidate drugs might therefore require use of live variola virus in the animal model.

15. **Vaccines.** The Committee reviewed new information on the safety and efficacy of three second- and third-generation vaccines. Clinical trials in human volunteers have produced excellent results in terms of vaccine efficacy. Evidence further suggested fewer adverse events in children, immunocompromised people, and people with dermatological disorders than seen with first-generation vaccines. Progress was considerable, and some companies would soon be able to manufacture large quantities of vaccine.

16. The Committee saw no need, for scientific reasons or regulatory purposes, for the use of live variola virus in animal models in order to assess smallpox vaccines.

17. **Proposals for future research.** The Committee recalled that its mandate was, under WHO's auspices, to oversee all research requiring use of live variola virus, to evaluate the essential nature of this research, to approve research proposals in this light, and to advise when the outcome of research has satisfied outstanding essential needs, thus providing the foundation for reaching consensus on the timing of destruction of variola virus stocks. As considerable research accomplishments had been noted at this and previous meetings, the Committee perceived an urgent need to review all proposals for further research against this progress in order to gain a clear perspective on what remaining work could be deemed essential. The Committee proposed that all current research proposals should be resubmitted for review. Such a procedure would transparently demonstrate that the Committee was performing its duty to provide oversight of all research involving live variola virus, as set out in resolution WHA55.15, and to ensure that all approved research is outcome-oriented and time-limited.

18. The Committee asked the Secretariat to identify a format for research proposals and establish a protocol and time frame for their submission to the Committee for its consideration.

19. **Expression of variola virus genes in other orthopoxviruses.** At the request of the Director-General, the Committee reconsidered the recommendation, made at its previous meeting, that the expression of variola virus genes in other orthopoxviruses was permissible provided certain stringent

conditions were met. After considerable debate, the Committee decided to withdraw this recommendation in its entirety.

20. In the discussion of this item at the 117th session of the Executive Board in January 2006, many speakers confirmed the need to ensure that all approved research remained essential, outcome-oriented, and time-limited. Some Board members felt that it was time to consider whether the benefits of destruction of the remaining stocks might not far outweigh those of continued research. The Board agreed that the Secretariat would prepare a draft resolution and convene a working group open to all members to examine the draft and make any necessary adjustments.¹ This meeting was held in Geneva on 5 April 2006.

21. After considering the recommendations of the Committee, the Director-General has decided to request it to review one matter at its next meeting, namely the specific areas in which further research involving live virus is not required. It is appreciated that in reaching its recommendations on this issue the Committee was looking at the current state of the science affecting the three areas concerned (sequencing, diagnostics and vaccines). The Director-General will ask the Committee to consider whether it may wish to retain the prerogative of recommending outcome-oriented and time-limited research proposals in these areas in the light of possible future scientific developments.

ACTION BY THE HEALTH ASSEMBLY

22. The Health Assembly is invited to consider the following draft resolution proposed by the working group.

The Fifty-ninth World Health Assembly,

Recalling resolution WHA49.10, which recommended a date for the destruction of the remaining stocks of variola virus, subject to a decision by the Health Assembly, and resolution WHA52.10, which authorized temporary retention of the virus stocks to a later date, subject to annual review by the Health Assembly;

Noting that the Health Assembly decided in resolution WHA55.15 to authorise further, temporary, retention subject to all approved research being outcome-oriented, time-limited and periodically reviewed, **and to a proposed new date for destruction being set when research accomplishments and outcomes allowed consensus to be reached on the timing of destruction of variola virus stocks** ~~with the objective of reaching consensus on a proposed new date for destruction of variola virus stocks when the research accomplishments and outcomes allow consensus to be reached on the timing of destruction of variola virus stocks;~~

Noting that authorization was granted to permit essential research for **global** public health purposes, including **further international research into** antiviral agents and improved and safer vaccines, and for high priority investigations of the genetic structure of the virus and the pathogenesis of smallpox;

¹ Document EB117/2006/REC/2, summary record of the fifth meeting.

Noting that resolution WHA52.10 requested the Director-General to appoint a group of experts [to oversee this research] **which will establish what research, if any, must be carried out in order to reach global consensus on the timing for destruction of existing variola virus stocks;**

[[Reaffirming]/[**Recalling**] the [view]/[**decisions**] of previous Health Assemblies that [the destruction of all variola virus stocks should remain the goal of WHO and all its Member States]/[**the remaining stocks of the variola virus should be destroyed**];]

[Recognizing that the destruction of all variola virus stocks is an irrevocable event and that the decision of when to do so must be made with great care;]

[**Recalling resolution WHA55.16, which called for a global public health response to natural occurrence, accidental release or deliberate use of biological and chemical agents or radionuclear material that affect health;**]

[**Further recognizing that unknown stocks of variola virus might exist, and that the deliberate or accidental release of those smallpox viruses would be a catastrophic event for the global community;**]

Having considered the report on smallpox eradication: destruction of variola virus stocks¹ and the report of the seventh meeting of the WHO Advisory Committee on Variola Virus Research;

Noting with satisfaction the [considerable progress]/[**success**] achieved in the development of [antiviral agents,] improved and safer vaccines, and sensitive and specific diagnostic tests, and in sequencing of entire genomes of viruses from numerous different strains, [**and that the WHO Advisory Committee on Variola Virus Research concluded that no further research requiring access to live variola virus was considered essential for these purposes;**]

[or]

[**Noting with satisfaction that considerable progress has been achieved in the development of antiviral agents, and that cidofovir and its analogues continue to be most promising compounds either already licensed or in advanced experimental studies;**]

[**Further noting with satisfaction that the WHO-led inspections in 2005 of the two authorized repositories reaffirmed the safety and security of the virus stocks;**]

Aware that no [new] antiviral agents for smallpox have been licensed, that live variola virus [will]/[**might**] be needed to ensure efficacy testing in vitro, and that further refinement of the animal model might be needed to make it more suitable for efficacy testing of these agents;

Noting that the WHO Advisory Committee at its seventh meeting perceived an urgent need to review [**with great care**] all proposals for further research using live variola virus against the considerable progress made to date;

¹ Document A59/10.

Further noting that the Secretariat, as requested by the WHO Advisory Committee, has identified a format for research proposals and has established a protocol and time frame for their submission to the Committee for its consideration, and that approved research is reported to WHO according to an established protocol;

[or]

[Welcoming the request of the WHO Advisory Committee, albeit only at its seventh meeting, that the Secretariat should identify a formula for research proposals and establish a protocol and time frame for their submission to the Committee for its consideration, and that approved research should be reported to WHO according to an established protocol, and thus not all research may have been adequately reviewed and reported to WHO according to any established protocol;]

1. STRONGLY REAFFIRMS the ~~view~~ **decisions** of previous Health Assemblies that the remaining stocks of variola virus should be destroyed;

2. FURTHER REAFFIRMS:

(1) the need to reach consensus on a proposed new date for the destruction of variola virus stocks[, **when research outcomes crucial to an improved public-health response to an outbreak so permit**];

(2) the decision in resolution WHA55.15 that the research programme shall be conducted in an open and transparent manner only with the agreement and under the control of WHO;

3. **DECIDES** that all essential research requiring live variola virus stocks for the purposes of sequencing, and development of diagnostics and vaccines has been completed, and that live variola virus stocks may no longer be retained for these purposes;]

[or]

[DECIDES to authorize further, temporary, retention of the existing stocks of variola virus up to, but no later than, 30 June 2010, at the current locations, for the purpose of research into antiviral agents, and to destroy all existing stocks of variola virus by no later than 30 June 2010;]

4. REQUESTS the Director-General:

(1) to continue the work of the WHO Advisory Committee on Variola Virus Research;

(2) to review the membership of the WHO Advisory Committee, and the representation of advisers and observers at meetings of this Committee, in order to ensure balanced geographical representation, with the inclusion of experts **from developing countries,[and] substantial representation of public health experts** ~~/[, also in public health, from developing countries]~~, **and the independence of the members of this Committee with respect to scientists at the two authorized repositories**];

- (3) to ensure that **[approved research proposals,]** research outcomes and the benefits of this research are made available to all Member States;
- (4) to maintain [regular]/**[annual]** inspections of the two **authorized** repositories in order to ensure that conditions of storage of the virus and of research conducted in the laboratories meet the highest requirements for biosafety and biosecurity;
- (5) **[To develop continually the operational framework for WHO's smallpox vaccine reserve; and]**
- (6) to continue to report annually on progress in the research programme[, **biosafety, biosecurity**] and related issues to the Health Assembly, through the Executive Board, **[and on implementation of the recommendations of the WHO Advisory Committee on Variola Virus Research accepted by the Director-General].**

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