World Health Organization

EXECUTIVE BOARD
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Smallpox eradication: destruction of variola virus stocks

Report by the Secretariat

1. In resolution WHA60.1 on smallpox eradication: destruction of variola virus stocks, the Sixtieth World Health Assembly requested the Director-General to undertake a major review in 2010 of the results of smallpox research already undertaken, research currently underway, and the plans and requirements for further essential research for global public health purposes. It was intended that, with this information, the Sixty-fourth World Health Assembly could reach consensus on the timing of the destruction of existing variola virus stocks.

2. In its decision WHA64(11) in 2011, the Sixty-fourth World Health Assembly strongly reaffirmed earlier decisions that the remaining stocks of variola virus should be destroyed. It also reaffirmed the need to reach consensus on a proposed new date for the destruction of the variola virus stocks, when research outcomes crucial to an improved public health response to an outbreak so permitted. The Health Assembly also decided, through the Executive Board, to include a substantive item "smallpox eradication: destruction of variola virus stocks" on the provisional agenda of the Sixty-seventh World Health Assembly.

3. This document reports the work undertaken by the Secretariat in preparation for the Sixty-seventh World Health Assembly. It summarizes the conclusions of both the Fifteenth meeting of the WHO Advisory Committee on Variola Virus Research (Geneva, 24 and 25 September 2013) and the second Advisory Group of Independent Experts to review the smallpox research programme (Geneva, 5 and 6 November 2013), and the recommendations of a meeting of the Strategic Advisory Group of Experts on immunization (Geneva, 5–7 November 2013). The latter Group based its conclusions and recommendations on the outcome of an expert consultation on smallpox vaccines and the WHO smallpox vaccine stockpile (Geneva, 18 and 19 September 2013).

SECRETARIAT ACTIONS

Review of variola virus research

4. The **WHO Advisory Committee on Variola Virus Research**, at its fifteenth meeting noted that the work under the authorized programme of research with variola virus had been performed

under its supervision. In 2013, 10 projects were evaluated by its scientific subcommittee and approved by the WHO Secretariat.[1]

5. The Advisory Committee received reports on the virus collections held at the two WHO Collaborating Centres that are the authorized repositories of variola virus: the State Research Centre for Virology and Biotechnology (Koltsovo, Novosibirsk Region, Russian Federation) and the Centers for Disease Control and Prevention (Atlanta, Georgia, United States of America).

6. The Advisory Committee was also provided with updates on the use of live variola virus for the development of diagnostic tests, one animal model, smallpox vaccines, and antiviral and therapeutic agents. Representatives of two pharmaceutical companies described candidate antiviral agents (tecovirimat and brincidofovir) that were at an advanced stage of development. Work is continuing on the studies needed to satisfy the requirements for regulatory approval. One pharmaceutical company provided an update on its vaccine that had been licensed in the 28 Member States of the European Union, Iceland, Liechtenstein and Norway in August 2013, with the indication for active immunization against smallpox of all adults.

7. Members of the Advisory Committee were asked to consider whether live variola virus was needed for further essential research on diagnostics, vaccines and antiviral agents against smallpox for public health benefit.

8. The majority view of the Advisory Committee was that no need exists to retain live variola virus for development of further diagnostics for smallpox or for the development of safer smallpox vaccines beyond those studies already approved.

9. The majority view of the Advisory Committee was that live variola virus was needed only for the further development of antiviral agents against smallpox.

10. The use to completion by the Centers for Disease Control and Prevention of 70 of its 420 variola virus stocks in the process of approved research has set a potential precedent for the progressive reduction of all live virus material being held in the two repositories, as a means of meeting the request of the Health Assembly.

11. The **Advisory Group of Independent Experts to review the Smallpox Research programme** met (Geneva, 5 and 6 November 2013) to review research with live variola virus during the period 1999–2013.

12. Members of the Advisory Group concluded that there is no need, from a global public health perspective, to retain live variola virus for any further research.

13. The reports of both the WHO Advisory Committee on Variola Virus Research and the Advisory Group of Independent Experts (document WHO/HSE/PED/CED/2013.3) were posted on the WHO website in December 2013.[1]

[1] Report of the Fifteenth meeting of the WHO Advisory Committee on Variola Virus Research (document WHO/HSE/PED/CED/2013.2, available online at http://www.who.int/csr/resources/publications/smallpox/WHO_HSE_PED_CED_2013_2/en/index.html, accessed 4 December 2013).

Recommendation of the Strategic Advisory Group of Experts on immunization on the size and composition the WHO smallpox vaccine stockpile

14. An expert consultation aimed at reviewing the scientific evidence on smallpox vaccines and proposing recommendations for the size and composition of the WHO smallpox vaccine stockpile was convened on 18 and 19 September 2013. Its conclusions and recommendations were presented to the Strategic Advisory Group of Experts on immunization in November 2013.

15. Members of the Strategic Advisory Group of Experts provided advice to the Director-General on which vaccines should be stockpiled and used as a response to an outbreak and for preventive use by laboratory personnel working with orthopoxviruses.

16. With respect to the size and composition of the WHO smallpox vaccine stockpile, members of the Strategic Advisory Group of Experts made the following recommendations.

- For the WHO stockpile, both the licensed ACAM2000 (second-generation) vaccine and LC16m8 (third-generation) vaccine are preferred. If they are not available, first-generation vaccines used during the campaign to eradicate smallpox (and derived from virus strains from lymph and the skin of animals) can be used.

- Countries donating vaccines to the WHO stockpile should provide the same vaccine that they hold in their domestic stockpile.

- In case of a smallpox outbreak, mass vaccination is not recommended, and vaccination should be limited to close contacts and first responders who have direct contact with symptomatic patients, and to laboratory workers expecting to have direct contact with specimens during their collection or processing.

- Given a total of 600–700 million doses of smallpox vaccine available in the world and that production capacity could rapidly reach up to 250 million doses per year, the current size of the WHO stockpile, including pledges, is appropriate for responding to an epidemic.

17. With respect to preventive use of the smallpox vaccines, the Strategic Advisory Group of Experts recommended that, based on a risk-benefit ratio, and the low risk of reappearance of smallpox, preventive vaccination should be limited only to laboratory personnel working with orthopoxviruses.[2]

LABORATORY NETWORK

18. As part of the process of establishing the laboratory network for diagnosis of smallpox and other orthopoxvirus infection, an ad hoc Independent Technical Group has been formed in order to agree on a standard diagnostic method for molecular diagnostics of orthopoxviruses and the molecular identification of variola virus. Terms of reference have been agreed for the laboratories in the network,

[1] Advisory Group of Independent Experts to review the smallpox research programme (AGIES), Report to the World Health Organization, Geneva, Switzerland, November 2013 (document WHO/HSE/PED/CED/2013.3, available online at http://www.who.int/csr/resources/publications/smallpox/WHO_HSE_PED_CED_2013_3/en/index.html, accessed 4 December 2013).

[2] For a summary report of the meeting, see http://www.who.int/immunization/sage/report_summary_november_2013/en/index.html (accessed 3 December 2013).

and criteria for inclusion of candidate laboratories have been defined. The Secretariat is identifying laboratories with the appropriate diagnostic capacities.

BIOSAFETY INSPECTION TO THE REPOSITORY SITES

19. WHO biosafety inspection teams visited the two variola virus repositories and inspected the containment facilities in the Russian Federation and the United States of America in 2012. The final reports of these biosafety inspections are available on the WHO web site.[1] The protocol that was used followed the European Committee for Standardization's Laboratory Biorisk Management Standard CWA 15793:2008, which covers 16 elements of laboratory biorisk management. The biosafety inspection visits of 2012 confirmed that this approach allows effective inspections of the repositories, helping to assure the wider community that the research therein is being done safely and securely, in line with the highest standards of biosafety and biosecurity. The next biosafety inspections of the two repositories of variola virus are planned for 2014.

DESTRUCTION OF CLONED VARIOLA VIRUS DNA IN SOUTH AFRICA

20. The Secretariat is finalizing arrangements for the destruction of cloned variola virus DNA fragments that have been stored in South Africa, including the visit date (planned for January 2014), composition of the team to witness the event, and the updating of the certification procedure set out in the Report of the Meeting of the Ad Hoc Committee on Orthopoxvirus Infections in 1994.[2]

OPERATIONAL FRAMEWORK OF WHO'S SMALLPOX VACCINE STOCKPILE

21. Work continues on an operational framework for access to WHO's emergency stockpile of smallpox vaccine in response to a smallpox event. The framework includes legal considerations for donating smallpox vaccines, standard operating procedures for donating countries as well as for recipient countries, logistical requirements, and a vaccine request form, with terms and conditions for the donation and reception of smallpox vaccines. The Secretariat has begun discussions with the national regulatory agencies of donating countries on the creation of a regulatory framework for the donation of smallpox vaccines.

ACTION BY THE EXECUTIVE BOARD

22. The Board is invited to note the report.

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[1] www.who.int/csr/disease/smallpox (accessed 3 December 2013).

[2] Document WHO/CDS/BVI/94.3.