World Health Organization

SEVENTY-SECOND WORLD HEALTH ASSEMBLY **A72/28**
Provisional agenda item 12.6 **4 April 2019**

Smallpox eradication: destruction of variola virus stocks

Report by the Director-General

1. In resolution WHA60.1 (2007) 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 undertaken and under way, and of the plans and requirements for further essential research for global public health purposes, for discussion at the Sixty-fourth World Health Assembly in 2011.

2. In its decision WHA64(11) (2011), following review of smallpox research undertaken, the Sixty-fourth World Health Assembly reaffirmed earlier decisions (resolutions WHA49.10 (1996) and WHA52.10 (1999)) that the remaining stocks of variola virus should be destroyed. It also reaffirmed the need to reach consensus on a proposed date for destruction of the variola virus stocks, when research outcomes crucial to an improved public health response to an outbreak so permitted.

3. At the Sixty-ninth World Health Assembly in May 2016, Member States discussed the timing of destruction of existing variola virus stocks. Given the advent of synthetic biology technologies, which make it possible to create variola virus using publicly available information and common laboratory procedures, the Health Assembly urged the WHO Advisory Committee on Variola Virus Research to review current research needs using live variola virus. It agreed that the Seventy-second World Health Assembly in 2019 would discuss a substantive agenda item on the destruction of variola virus stocks. Interim annual progress reports on the status of the research have been submitted to and noted by the Health Assembly.

4. This report provides an overview of the work undertaken by the Secretariat in preparation for the Seventy-second World Health Assembly. It summarizes the proceedings and conclusions of the twentieth meeting of WHO's Advisory Committee on Variola Virus Research (Geneva, 26 and 27 September 2018)[1] and provides an update on the status of the biennial biosafety inspections of the two authorized repositories of variola virus stocks: the WHO Collaborating Centre for Orthopoxvirus Diagnosis and Repository for Variola Virus Strains and DNA, State Research Centre for Virology and Biotechnology (VECTOR), Koltsovo, Novosibirsk Region, Russian Federation; and the WHO Collaborating Centre for Smallpox and Other Poxvirus Infections, Centers for Disease Control and Prevention (CDC), Atlanta, Georgia, United States of America.

[1] The report of the twentieth meeting of the Advisory Committee on Variola Virus Research (in press) will be posted on the WHO website on the following page: https://www.who.int/csr/disease/smallpox/resources/.

SECRETARIAT ACTIONS

Biosafety inspections of variola virus repository sites

5. Every two years, WHO biosafety inspection teams visit the variola virus repositories and inspect the containment facilities in the Russian Federation and the United States of America.[1] In the current round of biennial biosafety inspections of the repository sites, the team visited VECTOR between 28 January and 2 February 2019 and is scheduled to visit CDC between 20 and 24 May 2019; the same international team of biosafety experts, led by WHO, will undertake both inspections. The protocol used for the inspections follows the European Committee for Standardization Laboratory Biorisk Management Standard CWA 15793, which covers 16 elements of laboratory biorisk management. Reports of both inspections will be made available on the WHO website.

6. Successive biosafety inspections of the two repository facilities have found that the repositories meet international levels of biosafety and biosecurity, concluded that variola virus stocks remain in secure safekeeping, and made recommendations for ongoing improvement in biosafety in line with evolving knowledge and best practices.

Review of variola virus research

7. The Advisory Committee on Variola Virus Research at its twentieth meeting (Geneva, 26 and 27 September 2018) noted that the work under the authorized programme of research with live variola virus had been performed under its supervision. In 2018, 10 ongoing project proposals were assessed by the Advisory Committee and approved by the WHO Secretariat.

8. At its meeting, the Advisory Committee received reports on the work of the Secretariat during the year and reports from the two collaborating centres on the variola virus collections held in the repositories. The Advisory Committee reviewed the work of each centre and pharmaceutical companies cooperating in the authorized programme of research for the development of diagnostic tests, smallpox vaccines, and antiviral and therapeutic agents. The Advisory Committee also received reports on the status of the WHO Smallpox Vaccine Emergency Stockpile.

9. The Advisory Committee carefully considered both the progress made in ongoing research and the needs for future research requiring live variola virus. Most notably, having met all regulatory requirements, the antiviral agent tecovirimat was approved for treatment of smallpox by the United States Food and Drug Administration in July 2018. Tecovirimat is the first therapeutic compound approved for use against smallpox. The Advisory Committee noted continuing progress in the development of other antiviral agents, including brincidofovir and NIOCH-14, which are in advanced stages of pre-clinical and clinical trials, and monoclonal antibodies that neutralize variola virus more efficiently than vaccinia immune globulin.

10. The Advisory Committee noted the results of a successful non-inferiority trial for a third-generation vaccine with a better tolerability profile than existing vaccines, and progress towards the development of a more immunogenic and less reactogenic fourth-generation vaccine with an improved safety profile. It also noted advances in development of diagnostics: at VECTOR, a new multiplex real-

[1] For reports of the two previous biosafety inspections (in 2016 and 2017) see https://apps.who.int/iris/bitstream/handle/10665/272366/WHO-WHE-CPI-2018.14-eng.pdf and http://apps.who.int/iris/bitstream/handle/10665/272367/WHO-WHE-CPI-2018.15-eng.pdf?ua=, both accessed 22 February 2019).

time polymerase chain reaction technique for species-specific identification of human pathogenic orthopoxviruses and a new reagent kit; and at CDC, diagnostic assays specific for orthopoxviruses including variola virus in a multiplex format for automated diagnostic platforms using pre-packaged reagents, a protein-based assay based on monoclonal antibodies for variola virus detection in remote areas, and a variola-virus encoded protein microarray for use in evaluation of antibody responses.

11. The Advisory Committee acknowledged the benefits of variola virus research, including potential applications for prevention and control of monkeypox outbreaks, which are currently seeing a resurgence in Central and West Africa. The Advisory Committee welcomed the opportunity to review possible benefit of smallpox research for prevention and control of other orthopoxviruses, and reiterated its emphasis on the need for smallpox preparedness at the country and global levels, in particular the availability and accessibility of diagnostics and other related tools.

12. 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.

13. The majority view of the Advisory Committee was that no need exists to retain live variola virus for development of safer smallpox vaccines beyond those studies already approved. With regard to diagnostic assays essential for public health, members of the Advisory Committee were divided on the question of whether use of live variola virus remained necessary.

14. The majority view of the Advisory Committee was that live variola virus was still needed for the further development of antiviral agents against smallpox. It was particularly noted that it would be prudent and important to encourage the development and licensure of a second antiviral agent with a different mechanism of action from that of tecovirimat, the compound approved in 2018.

Implications of synthetic biology technology for the risk of smallpox resurgence

15. Members of the Advisory Committee recalled the conclusion in 2015 of the Independent Advisory Group on Public Health Implications of Synthetic Biology Technology Related to Smallpox[1] that the risk of re-emergence of smallpox has increased and continues to evolve. They noted that this reality was brought to the forefront by the de novo synthesis of horsepox virus, as reported to the Advisory Committee at its 18th meeting[2] in 2016, and the scientific report of which was published in a peer-reviewed journal in January 2018.

16. The distribution, handling and synthesis of variola virus DNA is governed by a series of recommendations made initially by the Ad Hoc Committee on Orthopoxvirus Infections and updated by the Advisory Committee on Variola Virus Research. The Independent Advisory Group on Public Health Implications of Synthetic Biology Technology Related to Smallpox had recommended that WHO's regulations for the handling of variola virus be revised to reduce and minimize the risk of a laboratory accident that might occur from the use of synthetic biology technology. Previous recommendations had therefore been updated in January 2016 to encompass the new realities related to synthetic biology

[1] The Independent Advisory Group on Public Health Implications of Synthetic Biology Technology Related to Smallpox: meeting report. Geneva: World Health Organization; 2015 (https://www.who.int/csr/resources/publications/smallpox/synthetic-biology-technology-smallpox/en/, accessed 22 February 2019).

[2] Advisory Committee on Variola Virus Research, 18th meeting (https://www.who.int/csr/resources/publications/smallpox/18-ACVVR-Final.pdf?ua=1, accessed 4 March 2019).

capacity.[1] At the Sixty-ninth World Health Assembly in May 2016,[2] Member States noted the Secretariat's report and commended the revision of WHO's recommendations concerning the synthesis and use of variola virus DNA. As noted in the guidance document, these recommendations are intended to be incorporated into individual Member States' biosafety guidelines or legislation.

17. At the twentieth meeting of the Advisory Committee on Variola Virus Research, members recalled the updated WHO recommendations concerning the distribution, handling and synthesis of variola virus DNA, as revised in 2016. These recommendations state that genetic engineering of variola virus and attempts to produce live virus from DNA are strictly prohibited, emphasize that any research using live variola virus must be performed in the maximum containment laboratory of one of the two global repository institutions and requires prior permission from WHO, and stipulate that no laboratory can hold variola virus DNA comprising more than 20% of the total genome other than the designated WHO Collaborating Centres hosting the variola virus repositories. The Advisory Committee nonetheless recognized the need for ongoing preparedness to deal with the potential consequences of the synthesis or possible re-emergence of variola virus.

Operational framework for the WHO Smallpox Vaccine Emergency Stockpile

18. In November 2013, WHO's Strategic Advisory Group of Experts on Immunization provided guidance on smallpox immunization policy and vaccine stockpile considerations. The WHO Smallpox Vaccine Emergency Stockpile consists of a physical stockpile of 2.8 million doses of vaccine held and managed in Switzerland by the WHO Secretariat, of which an inventory was completed in July 2018, and a pledged stockpile of 27 million doses held by the Member States: France, Germany, New Zealand and the United States of America. The United Kingdom of Great Britain and Northern Ireland provided a financial contribution to procure vaccine for the WHO physical stockpile. The stockpile consists of first-generation vaccinia virus vaccine (from a variety of sources, used during later years of the smallpox eradication programme), and a licensed second-generation vaccine (ACAM2000). Vaccines in both the physical and pledged stockpiles are periodically tested for potency.

19. The operational framework for the deployment of vaccine from the WHO Smallpox Vaccine Emergency Stockpile in response to a smallpox event[3] was published in December 2017. The framework outlines procedures for the deployment of smallpox vaccine (including diluent) and ancillary supplies (bifurcated needles and syringes for dilution) from the WHO Smallpox Vaccine Emergency Stockpile to recipient countries, legal considerations for such supply, logistical requirements, and a vaccine request form with terms and conditions to which the supply of smallpox vaccine to recipient countries is subject. The Secretariat is planning simulation exercises to test deployment procedures for emergency use of smallpox vaccines. The operational framework will be updated as preparedness and response planning