

Smallpox eradication: destruction of variola virus stocks

Report by the Director-General

BACKGROUND

1. The activities mentioned in this report are conducted within the framework of resolutions WHA49.10 (1996), WHA52.10 (1999), WHA55.15 (2002) and WHA60.1 (2007). In resolution WHA49.10, the Health Assembly set a date for destruction of variola virus stocks, subject to confirmation. In resolutions WHA52.10 and WHA 55.15, it authorized the retention of the existing stocks of variola virus on the understanding that steps should be taken to ensure that all approved research would remain outcome-oriented and time-limited. In resolution WHA52.10, authorization was granted to permit further international research into antiviral agents and improved vaccines, the genetic structure of the virus and the pathogenesis of smallpox.

2. In 2007, in resolution WHA60.1 (2007) on smallpox eradication: destruction of variola virus stocks, the Health Assembly affirmed the decision in resolution WHA55.15 regarding retention of variola virus in two WHO collaborating centre repositories and the manner of the research conducted to develop diagnostics, antiviral agents and vaccines for smallpox. It also requested the Director-General “to ensure that approved research proposals, research outcomes and the benefits of this research are made available to all Member States” and “to maintain biennial 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”. The Seventy-second World Health Assembly (2019) noted a progress report, having considered arguments and proposals to extend the research programme for up to five years and emphasized that the public health benefits of the research programme should be accessible to all.¹ The subsequent activities are in line with WHO’s Thirteenth General Programme of Work (2019–2025) to reach one billion more people better protected from health emergencies. Progress reports have been submitted annually to the Health Assembly.

3. This report provides an overview of the work undertaken by the Secretariat since 2019. It summarizes the conclusions and recommendations of the Advisory Committee on Variola Virus Research at its twenty-fifth meeting in October 2023 and provides an update on biennial biosafety and biosecurity inspections of the two authorized variola virus repositories: 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. This report also provides updates on WHO recommendations on smallpox immunization and on WHO’s response to the multi-country outbreak of mpox since 2022.

¹ See documents WHA72/2019/REC/3, summary record of Committee B, seventh meeting, section 2, and A73/32.

SECRETARIAT ACTIONS

Monitoring variola virus research

4. The Advisory Committee on Variola Virus Research at its twenty-fifth meeting (Geneva, 25 and 26 October 2023) received reports from the two collaborating centres on the variola virus collections held and assessed 12 new and ongoing project proposals. The Advisory Committee carefully considered the progress made and the needs for future research requiring live variola virus.

5. The Advisory Committee took into account the lessons learned from the COVID-19 pandemic and the global mpox outbreak, ongoing since 2022 and noted that the context in which smallpox preparedness must now be viewed has changed. Salient elements included the waning of immunity against smallpox in the global population, the advent of the HIV/AIDS pandemic and greater prevalence of other immunosuppressive conditions, the continuing advance of synthetic biology and biotechnology making de novo synthesis of viral pathogens possible, the continuing evolution of orthopoxviruses including genetic features suggesting adaptation to more efficient human-to-human transmission, and the observation that currently available countermeasures may not be sufficient to contain outbreaks in the face of a more transmissible and pathogenic orthopoxvirus.

6. The Advisory Committee noted advances in development of orthopoxvirus diagnostics and recommended that further research on point-of-care diagnostics suitable for use across all resource levels should continue, including efforts on rapid diagnostics for mpox. The Advisory Committee also continued to recommend, and the two WHO collaborating centres agreed, completion of the sequencing of remaining variola virus isolates, with the genome sequence data to be made available on public databases directly or through WHO.

7. The Advisory Committee further noted that, in continuing efforts to develop safer smallpox vaccines under the oversight of WHO, a non-replicating modified vaccinia Ankara (MVA) vaccine had been approved for prevention of smallpox, mpox and other orthopoxvirus infections.¹ (See also paragraph 12.) The attenuated minimally-replicating smallpox vaccine LC16 licensed in Japan in 1975 was approved in 2022 for prevention of mpox and other orthopoxvirus infections.² The first fourth-generation smallpox/orthopoxvirus vaccine (VacΔ6)³ was approved in the Russian Federation in November 2022 for prevention of smallpox, mpox, cowpox and vaccinia virus infection. The Advisory Committee was of the view that further development of scalable less-reactogenic vaccines such as mRNA vaccines to improve efficacy and durability of protection would be essential for the control of an outbreak of smallpox in the current context, should it recur.

8. With regard to research on antiviral therapeutics, the Advisory Committee noted that the antiviral agent tecovirimat approved for treatment of smallpox had also now been approved for treatment of mpox, cowpox and vaccinia virus infections in Europe in 2022, and that the antiviral agent NIOCH-14 had been approved in the Russian Federation in October 2022 for treatment of smallpox, mpox and other infections caused by orthopoxviruses. While commending progress and noting that effectiveness studies of antiviral agents for use in mpox are still underway, the Advisory Committee also noted research reports of antiviral resistance arising in a small proportion of patients who required prolonged treatment

¹ MVA-BN is the MVA vaccine developed and manufactured by Bavarian Nordic, Copenhagen, Denmark. It is marketed as Imvamune in Canada, Imvanex in the European Union and Jynneos in the United States of America.

² LC16 vaccine is based on the LC16m8 vaccinia virus strain, now manufactured by KM Biologics and known as LC16-KMB.

³ The vaccinia-virus based VacΔ6 developed by VECTOR with the oversight of the Advisory Committee since licensing also known as OrthopoxVac.

for mpox with tecovirimat, particularly those with compromised immune systems. Committee members observed that tecovirimat and NIOCH-14 share a similar mechanism of action and that brincidofovir may not be widely used owing to safety profile concerns. The Advisory Committee therefore expressed the view that multidrug therapy may be necessary to achieve clinical and public health objectives in the event of a smallpox outbreak and recommended that further research to develop small-molecule antiviral agents against orthopoxviruses should continue, including for smallpox.

9. The Advisory Committee acknowledged the benefits of variola virus research and discussed the requirements for use of live variola virus for ongoing research that arise from the recommendations noted above. It concluded that access to and use of live variola virus remain essential for implementation of these recommendations. The Committee expressed the view that development and licensure of additional antiviral agents would not be a short-term effort. The Advisory Committee also noted that preparedness for smallpox is currently inadequate, that equitable provision of countermeasures was not achieved during the global mpox outbreak, and that the global community must further invest in supporting access to resources arising from the variola virus research programme monitored by WHO.

10. Notwithstanding the recommendations of the Advisory Committee, the Secretariat reaffirms that, recalling that advances in synthetic biology and genome reconstruction technology may bring both benefits and risks for smallpox preparedness¹ and that the risk of smallpox re-emergence continues to evolve,² the distribution, handling and synthesis of variola virus DNA continue to be governed by WHO's recommendations to encompass these new realities.^{3,4} These WHO recommendations should continue to govern all work with variola virus DNA and are intended to be incorporated into Member States' biosafety guidelines or legislation.⁴

Biosafety inspections of variola virus repository sites

11. As mandated by the Health Assembly, WHO carries out regular biosafety and biosecurity inspections of the authorized variola virus repositories and containment facilities in the Russian Federation and the United States of America with a team of independent global experts, employing a protocol based on the European Committee for Standardization Laboratory Biorisk Management Standard CWA 15 793. The inspections took place at CDC in May 2022 and at VECTOR in October 2023. Successive inspections of the two facilities have found that the repositories meet international biosafety and biosecurity standards, that variola virus stocks remain in secure safekeeping, and that recommendations for ongoing improvement in biosafety continue to evolve with new technology, knowledge and best practices. Reports of all prior inspections are available on the WHO website.⁵

¹ WHO Advisory Committee on Variola Virus Research meeting reports, notably reports of the eighteenth (2016) and twenty-first (2019) meetings. (<https://www.who.int/groups/who-advisory-committee-on-variola-virus-research/meeting-documents>; accessed 10 November 2023).

² 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/publications/i/item/the-independent-advisory-group-on-public-health-implications-of-synthetic-biology-technology-related-to-smallpox>, accessed 10 November 2023).

³ WHO Recommendations concerning the distribution, handling and synthesis of variola virus DNA – revised 13 January 2016. Geneva: World Health Organization; 2016 (<https://www.who.int/publications/i/item/10665-241232>, accessed 10 November 2023).

⁴ Documents A72/28 and WHA72/2019/REC/3, summary records of Committee B, seventh meeting, section 2.

⁵ See reports of all biosafety inspections at: <https://www.who.int/emergencies/situations/smallpox/biosafety-inspection-reports>, (accessed 10 November 2023).

Guidance on immunization for smallpox and WHO vaccine reserves

12. In September 2023, WHO's Strategic Advisory Group of Experts on Immunization (SAGE) updated recommendations on smallpox vaccines, last discussed in 2013, in order to provide guidance on smallpox immunization for preventive use and for outbreak response and on the composition of the WHO vaccine reserve.¹ Smallpox vaccines currently available (see paragraph 7) are vaccinia virus-based and include first-generation vaccines produced in the lymph or skin of inoculated animals (for example, Dryvax, Lister strain vaccines or similar), second-generation vaccines produced in tissue cells (ACAM2000), third-generation vaccines based on minimally-replicating (LC16) or non-replicating (MVA) virus and a fourth-generation vaccine based on a vaccinia virus from which virulence genes had been deleted. SAGE also acknowledged that a range of vaccinia virus-based smallpox vaccines may continue to be stored or manufactured by Member States.

13. Following consideration of new information on the safety of smallpox vaccines, SAGE issued recommendations on their preventive use, with specific consideration of target populations, re-vaccination and choice of vaccines. SAGE also made recommendations on the choice of vaccine for use in outbreaks, including in previously vaccinated and special populations such as pregnant and immunocompromised persons for whom a non-replicating vaccine should be used. Further, SAGE recommended that Member States should develop or update response plans for a smallpox outbreak, considering a risk-based approach to vaccination and contingency plans to manage the outbreak with a constrained supply of vaccine.

14. The WHO smallpox vaccine reserves consist of 2.7 million doses of vaccine held and managed in Switzerland by WHO. They comprise first-generation vaccine (produced during later years of the smallpox eradication programme) and the licenced second-generation vaccine ACAM2000.² An inventory was completed in January 2023. Potency tests of the WHO physical vaccine reserves completed in 2022 showed that the vaccines retain their potency. A further approximately 28 million doses have been pledged by France, Germany, Japan (in progress) and the United States of America. In September 2023, SAGE provided recommendations on the choice of vaccines for the (physical and/or pledged) WHO smallpox vaccine reserve to add the third-generation vaccine, MVA-BN, to current reserves composed of first-generation, second-generation (ACAM2000), and third-generation (LC16-KMB) vaccines.

15. Previous WHO resources to support a response to smallpox cover an operational framework for the deployment of the WHO vaccine emergency reserves and a report on identifying and responding to serious adverse events following immunization in a public health emergency. During the global mpox outbreak, WHO also published guidance on how to use a bifurcated needle to perform multiple punctures for vaccination. In September 2023, SAGE noted that protocols for access to smallpox/mpox vaccines might require review.

¹ Highlights from the Meeting of the Strategic Advisory Group of Experts (SAGE) on Immunization 25–29 September 2023. (The full report will be published in the Weekly Epidemiological Record on 1 December 2023). Geneva: World Health Organization; 2023 (https://cdn.who.int/media/docs/default-source/2021-dha-docs/highlights-3.pdf?sfvrsn=9237c77d_1, accessed 10 November 2023).

² ACAM2000 was developed in collaboration with Sanofi-Pasteur and is now manufactured by Emergent BioSolutions.

WHO response to the public health emergency of international concern for the multicountry outbreak of mpox, as related to variola virus research

16. Since May 2022, an unprecedented multicountry outbreak of mpox emerged and was declared by the Director-General to constitute a public health emergency of international concern on 23 July 2022, which status was maintained until 10 May 2023. Member States have reported more than 92 000 laboratory-confirmed cases of mpox in 116 countries,¹ with many thousands more suspected (clinically compatible) cases in Africa where access to diagnostics remains limited. Countermeasures developed for smallpox were deployed by some Member States. The Secretariat provided extensive diagnostic support to countries in the form of polymerase chain reaction kits, undertook studies to validate commercially available supplies, initiated external quality-assurance mechanisms for mpox diagnostics, provided support for sequencing monkeypox virus strains, and issued target product profiles for diagnostics development. It also developed template protocols for assessment of antiviral therapeutic agents, procured tecovirimat for limited deployment for compassionate and emergency use, and supported coordination of bilateral and collective vaccine-sharing mechanisms.

17. For mpox, WHO considers that the outlook remains concerning with respect to recurrent outbreaks in all WHO regions and ongoing epidemic activity among long-affected ecological zones in Africa, most particularly in the Democratic Republic of the Congo where high numbers of cases continue to be reported and where sexual transmission of the more virulent clade I of the monkeypox virus has been documented in 2023. WHO is also concerned that the ongoing HIV pandemic as well as other factors that may lead to immunosuppression makes populations much more vulnerable to mpox, leading to higher risk of severe disease or death, and providing continuing opportunity for viral evolution and adaptation to human-to-human transmission of what was previously primarily considered to be a zoonotic disease. For these reasons, the Director-General issued standing recommendations to all Member States to maintain and strengthen mpox surveillance, to continue reporting of cases to WHO, to sustain prevention and control strategies through integration with other health programmes and services, and to develop national plans towards the elimination of human-to-human transmission of mpox.² With support from Member States, the Secretariat has outlined a WHO Strategic Framework for enhancing control and achieving elimination of human-to-human transmission of mpox (2023–2027).

18. The Secretariat is encouraged that smallpox medical countermeasures have been deployed by some Member States during the global mpox outbreak, thereby demonstrating the public health benefit that has accrued from years of research for smallpox preparedness. It is to be noted that funding for mpox response remains extremely constrained. The Secretariat encourages further studies on the effectiveness of countermeasures for mpox prevention and control and remains concerned about the still-limited access to diagnostics and the inequitable deployment of vaccines and therapeutics. The Advisory Committee on Variola Virus Research advised that the lessons learned from the global mpox outbreak should continue to inform planning for variola virus research, that mpox control efforts should be adequately resourced, and that work on countermeasures for prevention and control of smallpox and elimination of mpox should be pursued.

¹ Epidemiological data on mpox are updated here: https://worldhealthorg.shinyapps.io/mpx_global/ (accessed 10 November 2023).

² The WHO Standing recommendations for mpox issued by the Director-General (2023) can be found here: [https://www.who.int/publications/m/item/standing-recommendations-for-mpox-issued-by-the-director-general-of-the-world-health-organization-\(who\)-in-accordance-with-the-international-health-regulations-\(2005\)-\(ihr\)](https://www.who.int/publications/m/item/standing-recommendations-for-mpox-issued-by-the-director-general-of-the-world-health-organization-(who)-in-accordance-with-the-international-health-regulations-(2005)-(ihr)), accessed 10 October 2023)

ACTION BY THE EXECUTIVE BOARD

19. The Board is invited to note the report and consider the following questions:

- which avenues of research, if any, should be prioritized for ongoing development of countermeasures for smallpox and other orthopoxviruses?
- which actions can Member States propose to advance preparedness for outbreaks due to orthopoxviruses (which include smallpox and mpox)?

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