

Advisory Group of Independent Experts to review the smallpox research programme (AGIES)

Comments on the *Scientific Review of Variola Virus Research, 1999–2010*

December 2010

GLOBAL ALERT
AND RESPONSE



World Health
Organization

Advisory Group of Independent Experts to review the smallpox research programme (AGIES)

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Acronyms and abbreviations

ACVVR	WHO Advisory Committee on Variola Virus Research
AGIES	Advisory Group of Independent Experts to review the smallpox research programme
CDC	Centers for Disease Control and Prevention, United States of America
CPXV	cowpox virus
ECTV	Ectromelia/mouse virus
HIV	human immunodeficiency virus
MPXV	monkeypox virus
OPV	orthopoxvirus
PCR	polymerase chain reaction
RPXV	rabbitpox virus
SRC VB VECTOR	The Russian Federation State Research Centre of virology and Biotechnology
USFDA	United States Food and Drug Administration
VACV	vaccinia virus
VARV	variola virus
WHO	World Health Organization

Introduction

In May 2007, resolution WHA60.1 of the World Health Assembly requested the Director-General of the World Health Organization (WHO) to undertake a major review, in 2010, of the state of smallpox research and additional related research needed for public health purposes. This was undertaken so that the sixty-fourth World Health Assembly, in 2011, could come to a global public consensus on the timing of the destruction of existing variola virus (VARV) stocks.

In November 2008, the WHO Advisory Committee on Variola Virus Research (ACVVR) decided that a comprehensive review of the literature and of unpublished data concerning live variola virus research should be undertaken by a group of scientists endorsed by the Committee and representing all areas of research and development on orthopoxviruses (OPVs).

This resulted in the creation, under the supervision of the ACVVR, of a consolidated document entitled *Scientific review of variola virus research, 1999–2010* (hereinafter called ‘the Scientific Review’). The Scientific Review comprised six chapters.

1. Smallpox vaccines
2. Laboratory diagnostics for smallpox (variola virus)
3. Variola genomics
4. The status of WHO Collaborating Centre repositories of variola virus and nucleic acid
5. Animal models and pathogenesis
6. Antiviral drug development for the treatment of smallpox – status of small-molecule therapeutics.

This Scientific Review has now been considered by a group of independent experts from outside the variola virus field (the Advisory Group of Independent Experts to review the smallpox research programme, or AGIES). The AGIES was constituted by the WHO smallpox secretariat. The comments and subsequent recommendations of AGIES are summarized in this document.

Terms of Reference and Membership of the Advisory Group of Independent Experts to review the smallpox research programme (AGIES)

Terms of Reference

The Advisory Group of Independent Experts (AGIES) was formed to act as an advisory body to WHO on matters of strategy and evaluation of the smallpox research programme, with the following functions:

1. To read the document entitled *Scientific review of variola virus research, 1999–2010*, in order to:
 - I. Review the results of smallpox research already undertaken, and the plans and requirements for further research essential for global public health purposes.
 - II. Assess whether additional research using live variola virus is necessary from a global public health perspective.
2. To deliver a report to WHO at the WHO Advisory Committee on Variola Virus Research meeting (17 November 2010) summarizing achievements to date and additional work needed to ensure high standards of security related to a potential re-emergence of smallpox from a public health perspective.

Membership of AGIES

Members of the AGIES were selected and appointed by the Director-General of WHO to serve in their personal capacities, representing the broad range of disciplines relevant to the review of the smallpox research programme, while ensuring optimal diversification and balance of personal experience, professional background, gender, and geographical origin. For a full list of these members and their short biographies, see Appendix.

Declaration of Interests

In line with WHO policy all members of the AGIES have completed and signed a Declaration of Interests. One expert has declared a potential conflict of interest in the subject matter of this meeting. No relevant conflict of interests has been declared by the other experts. The declared interest reported by Gerd Sutter was assessed to be minimal and unlikely to affect, or to be reasonably perceived to affect, his judgment. However the Secretariat has determined that his declared interests should be disclosed. Professor Gerd Sutter's declared interest is as follows: the Institute for Infectious Diseases and Zoonoses, Ludwig-Maximilians-Universität München, where he works, has accepted research support from the German Government for a project relating to "Comparative Analysis of vaccinia viruses MVA as candidate next generation smallpox vaccines"; and BIOSAFE, a research consortium funded by the EC, for a project relating to deliberate releases of biological agents. This consortium includes the company Novartis Italy as one of the partners.

Executive Summary

AGIES found the *Scientific review of variola virus research, 1999–2010* to be clearly written and comprehensive, and to provide an accurate and up-to-date review of variola virus research, including the impact of regulatory restrictions on current and future research.

This full report is presented in three parts, in line with the terms of reference provided to the AGIES. In Part 1, a summary of each chapter of the Scientific Review is provided, followed by specific comments. Part 2 contains the committee's recommendations for further research and comments on variola virus (VARV) repositories. Part 3 summarizes AGIES recommendations for ensuring high standards of security related to re-emergence of smallpox.

Recommendations for further research and for use of live variola virus

Part 1. Genomics, diagnostics and repositories

Genomics

Near complete genomic sequences are available for approximately 50 isolates of variola virus. Since variola virus genome has only limited genomic diversity and shows major homologies with genomes of other orthopoxviruses, the AGIES feels that there is no public health need for sequencing of additional variola virus isolates.

Diagnostics

Several nucleic acid-based assays have been developed. Some have used cloned or synthetic genetic elements from variola virus DNA for assay evaluation and development, others have used intact genomic variola DNA; some have used cloned variola DNA as positive controls. Their further development does not require the use of live VARV.

In the absence of clinical disease, it is not possible to determine the sensitivity, specificity, positive and negative predictive value of these tests in clinical situations.

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