

## **Destruction of Smallpox Virus Stocks**

An Update on Developments since the Fifty-Ninth World Health Assembly  
*January 2007*

### **Introduction**

This short briefing prepared for the 120<sup>th</sup> Meeting of the WHO Executive Board (22-30 January 2007) provides an update on developments on the issue of destruction of smallpox virus stocks since the 59<sup>th</sup> World Health Assembly (WHA) in May 2006. To prepare this briefing we have relied upon open sources, the Report of the Eighth Meeting of the WHO Advisory Committee on Variola Virus Research<sup>1</sup> (WHO/CDS/EPR/2007.1<sup>2</sup>) held in November 2006, and the reports prepared for the Executive Board by the WHO Secretariat (EB120/39 and EB120/11).

### **Situation at the Close of the 59<sup>th</sup> World Health Assembly (WHA)**

The 59<sup>th</sup> WHA was unable to agree upon the text of a resolution on destruction of variola virus stocks, which are held in WHO authorized repositories in the US and Russia. Many developing countries, led by Africa, sought a resolution that established a destruction date for the virus (in June 2010), a prohibition on genetic engineering, annual substantive WHA review of virus research, and strengthened WHO oversight. France and the UK suggested that the WHA examine the unexplored question of the legal status of the virus stocks, by which was meant the ownership of stocks and other issues, including ownership of research results and products derived therefrom. Despite lengthy discussions, agreement was not reached. The US refusal to consider fixing a new destruction date was problematic, and developing country offers of a compromise were also rejected. As the 59<sup>th</sup> WHA drew to a close, the working group decided to defer further discussion until the 120<sup>th</sup> Meeting of the Executive Board.<sup>3</sup>

### **Recent Developments: Further Uncertainties About WHO Control of Variola Virus**

Since the close of the 59<sup>th</sup> WHA, two events have come to light – one scientific and the other political – that have heightened concerns that WHO’s control over variola virus is deteriorating.

First, Sandia National Laboratory (SNL), part of the US Department of Energy, has initiated experiments with variola virus genes engineered into other organisms. SNL’s historical mission is design and testing of nuclear weapons. SNL does not have a biomedical mission.

The variola genes obtained by SNL were inserted into other organisms in order to produce the proteins they encode for undisclosed purposes. SNL did not obtain the smallpox genes from a WHO-authorized repository. Instead, they were synthesized by a company and then used by SNL in at least four experiments. A request to the US government for further information on these experiments has not been answered. As SNL’s mission focuses on design and testing of Weapons of Mass Destruction (WMD) for the US armed forces, it is unclear if and how SNL research with variola virus genes was construed to be within the public health bounds established by WHA Resolution 52.10.<sup>4</sup>

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<sup>1</sup> In this paper and elsewhere, we refer to the WHO Advisory Committee on Variola Virus Research as the “VAC”, for Variola Advisory Committee.

<sup>2</sup> See: [http://www.who.int/entity/csr/resources/publications/WHOCDSSEPR2007\\_1.pdf](http://www.who.int/entity/csr/resources/publications/WHOCDSSEPR2007_1.pdf)

<sup>3</sup> For a more detailed review of discussions at the 59<sup>th</sup> WHA, please see our briefing “WHA Delays Decision on Smallpox Virus Stocks”, at <http://www.smallpoxbiosafety.org/who/whareport06.html>

<sup>4</sup> The SNL documents are available at <http://www.smallpoxbiosafety.org/sandia.pdf>

Secondly, a US government biosecurity committee has proposed that domestic US legal restrictions on possession of variola virus be repealed.<sup>5</sup> The *de facto* effect of this recommendation would be to legalize possession of variola virus. Although holding an exact copy of the entire virus in replication-competent form would remain subject to regulation,<sup>6</sup> possession of large amounts of smallpox DNA and construction and manipulation of viruses almost genetically identical to smallpox (i.e. essentially composed of variola genes) would not be subject to legal controls or even reporting to the government. Such viruses could pose an international public health threat. Moreover, as was demonstrated by SNL, it is now possible to acquire significant amounts of variola DNA through synthesis firms, and not the WHO repositories.<sup>7</sup>

These developments strongly suggest that an expansion of US research with variola virus is underway, particularly with variola genes and genetic engineering. ***They underscore the urgency of fixing a destruction date for the virus, of banning genetic engineering experiments, and of strengthening WHO control over variola research*** (see item on synthetic biology on page 3).

### **Comments on Issues Raised in the VAC Committee Report (2006) (WHO/CDS/EPR/2007.1)<sup>8</sup>**

*VAC Backpedaling on Virus Sequencing and Diagnostics:* At its seventh meeting in 2005, the VAC concluded that there is no justification for continued retention of variola virus for the purposes of sequencing (the full sequence of dozens of strains has already been obtained). Also at its seventh meeting, the VAC concluded that sufficient rapid and accurate diagnostics have been developed, with the majority of members in broad agreement that no additional research involving the use of variola virus is required for this purpose. The VAC may now be backpedaling on these decisions. It is reviewing the sequencing question by conducting a literature review of variola research. It is also assessing development of a new diagnostic in the US – which it did not previously deem essential.

These developments raise questions about the ability of the VAC to consistently prioritize public health and to resist pressure from certain members and advisors. In particular, paragraphs 4.2 and 4.3 of the report note that pressure for continued retention of live virus for sequencing of DNA is not for public health reasons, rather, it is because some researchers – almost certainly in the US<sup>9</sup> - consider the work “*scientifically interesting*”. Here the VAC is clearly in danger of losing its way. Its mandate is to permit and control only that research which is deemed essential for public health. Entertaining the intellectual interests of a few researchers is not essential for public health and is a completely inadequate reason to authorize continued retention of variola virus.

As we have previously suggested, the draft resolution under discussion should explicitly resolve that the WHA no longer authorizes the retention of variola virus stocks for the purposes of sequencing and development of diagnostics.

*Another VAC Retreat on Vaccines?* The VAC had also previously concluded that there is no longer any reason to retain smallpox virus for the purpose of developing vaccines. This is because in addition to older, effective vaccines, new vaccines are in advanced development. It had been concluded that these do not require variola virus for testing or production.

Now, however, the VAC may be reversing course on this decision because of a British study that raised a question about the strength of the immune response to the newer vaccines. The US is using variola virus in experiments designed to probe the parameters of the immune response to the new

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<sup>5</sup> This is the National Science Advisory Board on Biosecurity (NSABB). The recommendation is made in “Addressing Biosecurity Concerns Related to Synthesizing Select Agents” (Dec. 2006): <http://www.biosecurityboard.gov/news.asp>

<sup>6</sup> In the US, so-called “select agents” (potential bioweapons agents) such as variola virus are subject to the requirements of the Select Agent Rule (42 CFR Part 72, implementing Public Law 107-188, the Public Health Security and Bioterrorism Preparedness and Response Act of 2002) only if held in their entirety and in replication-competent form.

<sup>7</sup> To date, the repository in Russia reports that it has not transferred genes to other parties. The repository in the US has.

<sup>8</sup> In its substantive aspects, the Secretariat’s report to the Executive Board (EB120/39) is an abbreviated and somewhat simplified version of WHO/CDS/EPR/2007.1

<sup>9</sup> Almost certainly in the US because the report states “*Within the Russian scientific community, it was felt there was sufficient DNA already available to fulfill [sequencing] needs...*”

vaccines. It is not clear, however, if variola virus is essential, and no question has been raised about the older Dryvax vaccine, which prompts a robust and long-lasting immune response.

Effective vaccines for smallpox exist and do not require variola virus. It is imperative that the draft resolution explicitly resolves that it no longer authorizes the retention of variola virus stocks for the purpose of vaccine development.

*Animals Models and Antiviral Drugs:* The 8<sup>th</sup> VAC report describes largely the same animal and antiviral research as previous reports and no major movements forward are revealed. None of the underlying conditions that make this dangerous research unlikely to succeed have changed. Namely, according to the pharmaceutical industry, only one in 10,000 candidate compounds evaluated by drug companies is ultimately approved for sale and that approval, on average, takes 15 years to achieve. These figures include drugs for diseases that are more easily researched than smallpox, which has no human cases to observe and (experimentally) treat.

Thus, the odds remains heavily stacked against successful development and licensure of these proprietary compounds. This research is a greater risk than it is worth. Public health measures against variola should rely on destroying the virus (and banning its possession by anyone) and the availability of effective diagnostics and vaccines.

The draft resolution should thus terminate animal model research that uses live variola virus, in favour of a safer monkeypox-based model.

*VAC Proposal Review and Unauthorized Research:* In the past, the VAC had neglected its duty to identify, review, and – if merited – approve all research involving variola virus. Although details contained in the report are insufficient to draw a firm conclusion, it appears that the VAC has made some progress toward creating an effective review system. This possible progress, however, is offset by two factors. First, the VAC is reviewing projects through an unaccountable scientific subcommittee whose deliberations are unreported. Secondly, it appears that unauthorized retention of and research involving variola genes has taken place. The VAC report and EB 120/39 blandly put it “*concerns have been raised that WHO’s restrictions on the manipulation of variola virus genes may not be known in the wider scientific community.*”

Even if modest progress has been made in committee formalities, a review system that fails to identify and assess all relevant research would remain seriously flawed. To rectify this problem, project review should be conducted by the VAC itself and not by a small subcommittee, although a subcommittee could still help by preparing relevant written analysis for VAC consideration. Detailed summaries of proposed variola virus projects should be made available on the VAC web page prior to their review (and not after the research is conducted and published).

For these reasons, the proposals in the draft resolution for the WHA to receive a detailed report of the research that has been completed, is being undertaken and is being planned would also provide needed strengthening of the review process.

*Genetic Engineering and Changes to Existing Restrictions on Variola Virus Possession:* The VAC also revisited the question of modifying the rules concerning possession and use of variola virus and its genes. These rules touch on both genetic engineering and issues raised by synthetic biology. The rules<sup>10</sup> were put forward in 1994 by the WHO Ad Hoc Committee on Orthopoxvirus Infections, which was led by veterans of WHO’s successful drive to eradicate natural transmission of the virus, perhaps the Organization’s greatest achievement. They ban genetic engineering of variola, the insertion of variola genes in other orthopoxviruses, and require that variola DNA only be provided to non-repository labs with WHO approval and even then in tightly limited quantities.

For years, the United States has sought to weaken those rules. In 2004 it almost succeeded when the VAC recommended modification of the 1994 rules to permit dangerous experiments involving insertion of smallpox genes into related poxviruses and genetic engineering of smallpox itself. These recommendations were rejected by the 58<sup>th</sup> WHA in 2005 and the recommendation to permit insertion of smallpox genes into related poxviruses was subsequently withdrawn by the VAC.

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<sup>10</sup> Contained in WHO/CDS/BVI/94.3, available here: [http://whqlibdoc.who.int/hq/1994/WHO\\_CDS\\_BVI\\_94.3.pdf](http://whqlibdoc.who.int/hq/1994/WHO_CDS_BVI_94.3.pdf)

At the 8<sup>th</sup> VAC meeting in 2006, the US again expressed its desire to genetically engineer smallpox genes into other orthopoxviruses (see pp. 11-12). This proposal was rejected by the committee.

But the same rules that prohibit such smallpox genetic engineering also govern possession of smallpox genes by non-repository labs. After abandoning the 2004/05 recommendations to weaken the 1994 rules, in 2006 the VAC has started a new process that may modify them. This time, the effort has been reportedly prompted by synthetic biology, specifically disagreement over if and how the WHO should control synthesized variola genes. Some on the committee would take a permissive approach, while others were concerned about experiments such as those at Sandia, and that WHO restrictions on possession of smallpox DNA were insufficiently known among scientists.

The current rules state that the repositories cannot distribute smallpox DNA without WHO approval and that recipients of such DNA cannot send it to others. These provisions are appropriate and should remain. In view of the VAC's prior recommendations, now withdrawn, to weaken the 1994 rules, the process that the VAC has again initiated to review and possibly revise them again may prove dangerous and should proceed very cautiously and transparently, if at all.

The draft resolution before the Executive Board must therefore ensure that any research undertaken does not involve genetic engineering of the variola virus and prevents distribution of variola DNA for non-diagnostic purposes.

Another approach to address variola synthetic biology risks would be for the EB to ask the VAC to leave the 1994 recommendations intact and for the WHA to instead pass a smallpox resolution containing language that specifically addresses the synthetic biology risk. Elements for this resolution are presented below:

*Recommendations on Synthetic Biology:* It is impossible to ignore the report's contradictions with respect to synthetic biology. Section 3 of the 8<sup>th</sup> VAC report details the elaborate biosafety and biosecurity measures that protect virus stocks at the repositories. Yet Section 9 mentions the problems posed by synthetic variola genes made and held outside of the repositories. This problem is tangibly demonstrated by the variola gene experiments at Sandia National Lab, in which the genes were manufactured by a commercial provider. Obviously the importance of the protections at the repositories will become very limited if synthesis of variola genes is permitted elsewhere.

To address this problem, we suggest that WHA resolve that the: 1) Synthesis of variola virus genes outside of the WHO authorized repositories is prohibited, and; 2) Variola genes may only be transferred out of the WHO authorized repositories after WHO's permission has been obtained, and; 3) WHO shall only grant such permission on a case-by-case basis, and; 4) No work with variola virus genes shall be authorized outside of WHO authorized repositories unless a compelling reason is demonstrated why the research cannot be conducted within the repository, and; 5) That all such genes transferred shall be immediately destroyed upon completion of the research or upon WHO request, whichever is sooner.

*Questions of Timing:* The current research authorization procedure that the VAC uses is flawed. The VAC subcommittee is authorizing some research for 2 years, typically expiring on 31 December of a particular year. However, the VAC meets annually in November, meaning that its meetings are not sequenced in an appropriate way to review and approve/deny the research portfolio. This places too much discretion in the hands of the very small scientific subcommittee, which has a poor track record and is not large enough to adequately represent the various geographic, scientific, and public health interests relevant to decision-making.

This disconnection between the VAC subcommittee approval process and the meetings of the VAC itself is not conducive to the operations of a committee that aims to tightly control variola research in the interim before destruction of the virus. The research review and approval process needs to be better integrated into the WHO's and WHA's schedules. Approvals should only be for one year, and they should expire at the time of the VAC meeting, which should enable full committee review of all proposed projects and fast escalation to the Executive Board and WHA if necessary.