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Update on Destruction of Variola Virus Stocks (March 2006)

This paper provides an update on developments since publication of our 2005 paper, *The Genetic Engineering of Smallpox* (available at www.smallpoxbiosafety.org). It takes into account events from the 58th World Health Assembly (May 2005) through the present, including the report of the 7th Meeting of the WHO Variola Advisory Committee (November 2005) and the January 2006 meeting of the Executive Board (EB117/33). Prepared prior to the April 5, 2006 meeting of the *WHO Intergovernmental Working Group of the Executive Board on Smallpox Eradication: destruction of variola virus stocks*, key goals are indicated for a WHA resolution on destruction of variola virus stocks at the 59th World Health Assembly (WHA) in May 2006. For the latest information about this campaign, please visit www.smallpoxbiosafety.org or contact our offices.

Summary of Key Points

• There is broad agreement that variola virus stocks are no longer needed for sequencing, diagnostics, or vaccines. WHA authorization to retain virus stocks for these purposes can and should be withdrawn.

• The WHA has authorized essential research on antiviral drugs and an animal model of human smallpox infection. Determining what is essential requires balancing the public health risks and the probability of failure against the possible benefits.

• With respect to the animal model, dangerous research to expose monkeys to large amounts of virus to attempt to develop a model that would be of questionable value is not essential. A safer model using monkeypox virus shows promise. Efforts should focus on the monkeypox model and use of smallpox virus should be stopped.

• There are two antivirals under active consideration. In the US, one in 10,000 drug compounds is eventually approved for use. The process takes an average of 15 years. This suggests a one in 5,000 chance of success by about 2020. When balanced against the risks of an accident and high probabilities of failure, and taking into consideration the existence of rapid diagnostics and effective vaccines, this antiviral research is not essential.

• The 2005 proposal to allow expression of smallpox genes in related poxviruses has been abandoned, but the proposal to genetically engineer smallpox remains alive. This dangerous proposal should be stopped.

• WHO's Variola Advisory Committee (VAC) has made gestures towards reforming itself; but they are weak and come too late. The VAC has been lax and ineffective and must be rebuilt from the ground up in order to fulfill its mandate. From its seventh meeting it has emerged that the VAC:

- Has not seriously addressed criticism of its geographic and scientific imbalances nor its lack of transparency;
- Has operated since 1999 without establishing even basic elements of a proper oversight regime, such as formats for proposals and protocols and procedures for review of research.
- Has failed to track distribution of variola DNA fragments by the US Centers for Disease Control.
- Has asked the US and Russia for descriptions of ongoing research, begging the question, how can it be effectively controlling and overseeing research of which it has no detail?

Goals for a WHA Resolution in 2006

1. End WHA authorization to retain variola virus stocks for sequencing, diagnostics, and vaccines.

2. Terminate animal model research that uses smallpox virus in favor of a safer monkeypox-based model.

3. Establish a 2008 deadline to complete research on antiviral drugs that utilizes live smallpox virus.

4. Prohibit genetic engineering of smallpox virus by instructing the VAC to reject any such experiments.

5. Prohibit distribution of smallpox DNA except distribution of small segments necessary to maintain a small number of specialized diagnostic laboratories.

6. Replace the VAC with a more geographically and scientifically balanced body that will fulfill its WHA mandate to control smallpox virus research.

SUMMARY OF SMALLPOX STOCKS ISSUES AT THE 59TH WHA (MAY 2006)

BACKGROUND: The World Health Organization (WHO) is justly proud of the global effort that brought about the eradication of smallpox in 1977; but the truth of the matter is that the job was never finished. The United States and Russia still retain smallpox virus (*Variola*), an easily transmitted disease and ancient scourge of humanity that is a potent biological warfare agent. Smallpox kills one quarter or more of the people that it infects and leaves many who do not die disfigured and blind.

In 1999, the remaining stocks of smallpox virus were slated for imminent destruction. But Russia and the US balked at the World Health Assembly (WHA) resolution calling upon them to destroy the virus. Instead, they have accelerated smallpox research.

A controversial US plan to genetically-engineer the virus was debated at the WHA in 2005, and approval could come this year. Also last year, a proposal to allow smallpox genes to be expressed in related poxviruses was stopped after it was questioned by the Secretary-General and opposed by governments and NGOs. A plan to allow unlimited distribution of segments of smallpox DNA is also controversial. It has not yet been implemented. If these proposals are not stopped altogether, however, serious biosafety risks will be created, and the road to an artificial reconstruction of the virus for biowarfare purposes will be opened.

There is broad agreement that no valid reason exists to retain smallpox virus stocks for DNA sequencing, diagnostic tests, or vaccine development. More than adequate sequence data has been obtained and rapid and accurate diagnostic tests have been developed to identify any future outbreak. Licensed and candidate vaccines can protect against outbreaks and do not require live smallpox virus for their manufacture or testing.

Nevertheless, the US is pursing an aggressive research agenda related to development of new antiviral drugs. It is this research program that poses the largest obstacle to the final eradication of live smallpox virus. It is for this purpose that the US proposes to genetically engineer smallpox, and it is why the US is conducting dangerous experiments to inject monkeys with large amounts of the virus.

The risks of this research far outweigh its potential benefits. Not only is it unclear if the antiviral experiments will ever be successful, they are not essential because existing vaccines are effective and diagnostics rapid and accurate. The experiments could result in catastrophic lab accidents or other release of the virus. The genetic engineering experiments present particular biosafety risks including the possibility of creating an even more dangerous virus.

As if the world is condemned to repeat history through forgetfulness, since 2001, WHO political will to finish the job of smallpox eradication has faltered. Much of the blame can be laid at the feet of WHO's decision to leave oversight of smallpox research in the hands of a politicized "technical" advisory committee that has been dominated by a small number of countries and scientists with a personal interest in pursuing smallpox research.

The committee has been a failure. It has not controlled smallpox virus research and needs to be replaced. It has not been geographically and scientifically balanced. It has not diligently reviewed research proposals. It has not restricted experiments to those that are essential. The failure of this committee has weakened international control over smallpox virus stocks and has permitted a dangerous expansion of live smallpox virus research. The failure of this committee has distanced the world from the final destruction of smallpox virus stocks.

Discussions at the WHA in 2005 resulted in WHO taking some steps to try to reassert control over smallpox virus research. This modest movement is encouraging; but more needs to be done by governments to re-establish WHO control over smallpox virus research and to bring about destruction of the virus stocks. The Committee is only now attempting develop basic oversight procedures that should have been in place years ago, such as insisting that US and Russian researchers submit their proposals for review, and defining procedures for determining if proposed experiments are, in fact, essential.

Contained to only two labs in Russia and the US, smallpox has a multilateral research oversight structure that has no parallel with any other disease. WHA approval of any genetic engineering of smallpox would be perceived as encouragement for other genetic engineering experiments with exceptionally dangerous pathogens. No multilateral system yet exists for control of those disease agents. Globally, the number of high containment facilities handling dangerous disease agents is expanding and the hazardous applications of biotechnology are increasing. These trends are reflected in a growing number of lab accidents in a variety of countries in recent years involving highly pathogenic agents in high containment facilities.

POLICY DEVELOPMENTS IN 2005: At its 6th meeting in November 2004, the WHO Advisory Committee on Variola Virus Research (the Variola Advisory Committee, or "VAC") approved a controversial set of recommendations to permit genetic experimentation with smallpox virus and distribution of viral DNA. In January 2005, the Executive Board sent the recommendations to the 58th World Health Assembly (WHA).

Because of public controversy over the recommendations, in early 2005 the WHO Director General announced that he would conduct a study of the issue. In April 2005, weeks before the WHA began, he asked the VAC to reconsider one of its recommendations. The item would have allowed experiments to insert smallpox genes into other orthopoxviruses, such as monkeypox or mousepox. The Director General's request effectively halted WHA consideration of that single item in 2005; but it did not modify the other controversial recommendations, including that to permit genetic engineering of smallpox itself.

At the beginning of the 58th WHA, public statements by WHO defended the VAC, despite rising international controversy over its failure to properly oversee smallpox virus research. Inexplicably convinced that few people or governments were concerned about research risks and WHO's deteriorating control, WHO told journalists that genetic engineering of smallpox was a minor agenda item whose approval would "*take only five minutes.*"

In fact, discussions were much longer and concern greater than WHO predicted. Interventions lasted much of one afternoon and the following morning. The US and Russia defended their research, while more than two dozen other countries took the floor, mostly voicing concerns and opposition to the VAC recommendations.

South Africa called for research to be stopped while a WHO task team evaluated the smallpox virus research agenda and the VAC itself. Canada was not confident that the antiviral research was essential. Tonga noted that biomedical researchers are normally well-intentioned, but that a "bad apple" among those handling smallpox virus could be catastrophic. China called for stronger WHO oversight and, with countries including Cuba and Saudi Arabia, for a new date for smallpox virus stocks to be destroyed. The Netherlands questioned if safety precautions were adequate and, like Pakistan and others, recalled recent laboratory accidents to help make its point. Thailand and the UK stressed the need for research to be essential, outcome-oriented, and time-limited.

Responding on behalf of the WHO Secretariat, Assistant Director General of Communicable Diseases Dr Asamoa-Baah said the Secretariat took note of the Russian and US interventions. It also took special note of the "*concerns and caution*" articulated by a large number of countries (which he named). He added that the Secretariat especially welcomed the views, that with regard to the committee's recommendations, that the VAC "*revisit and review their recommendations*".

After events at the WHA, the VAC met for a seventh time on 10 and 11 November 2005. At the opening of the meeting, it was stressed by WHO staff that the situation had changed since the sixth meeting, and that pressure was building to end the research program. Despite the concerns raised at the WHA and Dr. Asamoa-Baah's reply, the VAC did not reconsider all of its recommendations. It only reconsidered the item on insertion of smallpox genes into other orthopoxviruses. After debate, it withdrew this recommendation in its entirety.

According to the report of the meeting, the VAC did not discuss genetic engineering of smallpox itself. There is no indication that any such experiments were reviewed or approved, however, VAC's oversight of smallpox virus research is so weak that the lack of discussion does not necessarily indicate the absence of experiments.

The VAC asked the US and Russia to submit their proposals for all ***ongoing*** and proposed research involving live smallpox virus, and for the two countries to provide results of completed experiments. This request reveals that the VAC is not confident that its entire membership is even aware of relevant activities at the smallpox labs. The VAC also asked the Secretariat to develop a format for research proposals and procedures to review those proposals. This was another striking request, as it reveals that the VAC has not yet developed procedures for proposal review and research oversight. Finally, the report indicates that the US distributed segments of smallpox DNA and that WHO does not know where this DNA was sent and how it has been utilized.

While the VAC's attempt to assert some authority might be viewed as a step in the right direction, the backdrop is alarming. WHA Resolution 52.10 states that all research "*shall be conducted in an open and transparent manner only with the agreement and under the control of WHO*". If no rigorous research review procedures were developed by the VAC from its establishment in 1999, how can it have lived up to the WHA's mandate? The VAC does not apparently even possess complete summaries of ongoing experiments and the results of all previous ones. Has unmonitored research taken place? Why don't WHO and the VAC know where the US sent smallpox DNA? These uncertainties and the VAC's unwillingness to assert authority are strong arguments for the WHA to replace the ailing VAC with a mechanism that will obey and implement the WHA's mandate.

At the meeting, the VAC concluded that enough smallpox gene sequences have been obtained (the US has sequenced at least 40 strains), and that adequate diagnostic tests have been developed. Thus there is no reason for retention of smallpox virus stocks for either sequencing or diagnostic tests. The VAC also reached this conclusion in 2004. The 7th VAC meeting also concluded that existing vaccines and candidate vaccines that are in late stages of development are sufficient and that there is no need for live smallpox virus to test these vaccines. This means that there is also no reason for retention of smallpox virus stocks for vaccine purposes. It remains to be seen if Russia and US will still accept this conclusion at the WHA in May 2006.

As there is no need for live smallpox virus for sequencing, diagnostics, or vaccines, then the only remaining reasons for retention of live smallpox virus are development of an animal model of human smallpox infection and a search for new antiviral drugs.

Smallpox was eradicated through public health monitoring and targeted vaccination campaigns, not with antiviral drugs. Currently, the US is focused on two compounds for possible use against smallpox. According to PhRMA, the pharmaceutical industry trade group, 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 far more easily researched than smallpox, which has no human cases to observe and (experimentally) treat. Thus, the odds are heavily stacked against the candidate antivirals.

Moreover, experiments to develop a monkey model of smallpox infection using live smallpox virus have not gone well. Monkeys that have been administered live virus in the US have required very large dosages to contract smallpox, and the progression of the disease in the primates has not closely resembled that in humans. A useful model may never emerge, no matter how many monkeys are inoculated with the virus and no matter how many dangerous iterations are made of variants on this experiment.

Smallpox virus may not even be necessary for an animal model. Monkeypox infection in monkeys shows promise as a model of human smallpox infection, and it does not require live smallpox virus. Rather than continuing to pursue dangerous research with primates and live smallpox virus, research efforts should be shifted to the far less risky route of an animal model using monkeypox.

The US has recently argued that an animal model and other tests requiring live smallpox may be necessary in order to gain antiviral drug approval from the US Food and Drug Administration. Given the existence of effective vaccines and diagnostics, and the difficulties of research, it is questionable if new antiviral drugs can continue to be deemed "essential". Because smallpox virus does not pose any significant risk of natural re-emergence, and stocks are limited to two laboratories, if one of the candidate antivirals advances, strong arguments can be made that US regulatory authorities should use alternative means, potentially including different kinds of testing, waivers, or conditional approvals for any smallpox antivirals. Everywhere in the world, such drugs would only be used under exceptional emergency circumstances.

In January 2006, the WHO Executive Board considered a summary of the VAC's 7th Meeting (EB117/33), which is a shortened version of the committee's full report (WHO/CDS/EPR/2006.2). Discussions included a request from African Member States for a resolution on destruction of variola virus stocks to be prepared for the 59th WHA (May 22-27). To further discuss the issue, the *WHO Intergovernmental Working Group of the Executive Board on Smallpox Eradication: destruction of variola virus stocks* was established. This group meets in Geneva on April 5th and will consider points of a possible resolution.

STEPS FOR THE 59TH WHA: The devastating effects of the smallpox virus and the hundreds of millions of victims of this deadly pathogen are increasingly forgotten. One step at a time, the WHA has moved from destruction of smallpox virus to retention of stocks, to limited research, and now to genetic engineering. At the 59th WHA meeting, Member States should act to put the virus back on a fast track to final eradication.

A successful WHA in 2006 will both take steps to narrow the research agenda and to strengthen international oversight, thereby stepping closer to destruction of smallpox virus. To improve oversight, the existing VAC should be disbanded, and a new committee constituted with geographic and scientific balance, increased transparency, and a firmer will to implement WHA's mandate to control any approved smallpox virus research.

To more quickly bring about an end to research and destruction of the virus stocks, the WHA should pass a resolution that rescinds its temporary authorization for retention of virus stocks for sequencing, diagnostics, and vaccines. The resolution should also terminate research for an animal model that utilizes smallpox virus, in favor of one using monkeypox. Antiviral drug research utilizing smallpox virus should be permitted only until a prompt deadline, and under no circumstances should WHA approve genetic engineering of smallpox or the distribution of smallpox DNA except for that necessary to maintain a small number of diagnostic labs.