

SMALLPOX ERADICATION: DESTRUCTION OF VARIOLA VIRUS STOCKS

Issues for the 130th Session of the WHO Executive Board, January 2012

Third World Network

The following brief summarizes key issues on variola virus for the WHO Executive Board's 130th Session, beginning in Geneva on 16 January 2012. This information is based upon review of the Secretariat's progress report (EB 130/35 Add. 3) and the Report of the Thirteenth Meeting of the WHO Advisory Committee on Variola Virus Research (WHO/HSE/GAR/BDP/2011.2).

Background

Smallpox was eradicated more than 30 years ago. The long-planned but postponed destruction of the remaining smallpox virus stocks, held at authorized WHO Repositories in the US and Russia, has taken on greater urgency in the last 7 years. All research with these WHO virus stocks, which were collected in dozens of countries around the world, must be approved by WHO and is limited to specific World Health Assembly (WHA) authorized research that is essential for global public health.

In 2005, governments and civil society groups worldwide were alarmed when the US won approval from the WHO Advisory Committee on Variola Virus Research (ACVVR) to genetically engineer the smallpox virus and to insert smallpox genes into related orthopoxviruses. Following debate, including at the World Health Assembly, the ACVVR's approval for these experiments was withdrawn, and at the urging of Member States, WHO stepped up its lax oversight of variola research, improving the regional balance of Committee members and the transparency of the ACVVR's operations.

In 2006 at the WHA, a debate on destruction of the stocks - which the US and Russia wish to keep - resulted in a compromise agreement to conduct a review of the smallpox research program. This Major Review was tabled at the 64th WHA in 2011, and included a report by WHO public health experts that found no compelling public health reason to keep the viruses. A scientific review, largely authored by US and Russian government scientists, was less clear in its conclusions, but also did not identify any essential reason to keep the virus.

Despite the conclusions of the Major Review, at the 64th WHA the US and Russia insisted on keeping the virus stocks, with the US introducing a resolution that would have amounted to permission to keep the virus indefinitely. But other countries, particularly in the Middle East and North Africa, opposed the US draft resolution and instead proposed that a specific date for virus destruction be fixed.

The result was a compromise to defer the destruction discussion for three years, until the 67th World Health Assembly in 2014. The compromise also provides for future meeting(s) of WHO's Advisory Group of Independent Experts (AGIES), the WHO public health expert group that concluded, in 2011, that there are no compelling public health reasons to keep the virus.

In the meantime, the WHO authorized research program using variola virus continues, with the ACVVR taking the lead on its oversight, and reporting back to the WHA annually until the issue is again taken up as a substantive WHA agenda item in 2014.

WHO Losing Control Again?

The 2011 Major Review effectively concluded that the WHO-authorized research program had reached its end (or, in the US and Russian view, has made great progress). This would suggest that both the scope and number of active variola projects approved by WHO should be declining towards zero, because the need for new research is minimal and, in some cases (such as sequencing), indubitably satisfied.

The report of the ACVVR's meeting on late 2011, however, shows that the actual trend is the opposite. The ACVVR continues to approve a wide array of projects utilizing variola virus, including research in areas that it (and the Major Review) have previously concluded no longer require the virus. In fact, it appears as if WHO may be once again losing control over smallpox research - as was the case in 2005 when the US pushed the (subsequently cancelled) smallpox genetic engineering experiments through the committee.

Frequently, WHO's problem is ACVVR not acting in accordance with its own scientific determinations. Where the ACVVR (and AGIES) have concluded that no additional research is essential for public health (e.g. diagnostics), or that research is not worthwhile (e.g. the animal model), the committee paradoxically continues to approve new projects. These contradictions are more than a scientific embarrassment to the flip-flopping committee, they seem to indicate that WHO isn't really in control.

Therefore, at the 130th Executive Board and the 65th World Health Assembly, it is important for Member States that favor prompt destruction of smallpox virus stocks to note their concern with WHO's growing impotence and to emphasize the need to rapidly wind down research and for WHO to assertively apply WHA decisions.

A review of the report of the ACVVR's 2011 meeting provides some opportunities to highlight this:

US Company Flouts WHO Rules: Underscoring WHO's weakness, a US company was found to have inserted a short segment of smallpox DNA into a related orthopoxvirus. This experiment was a violation of WHO rules that expressly prohibit such genetic engineering with smallpox and its genes. The report provides only scant detail of the incident, and states that the unnamed company was requested to destroy the engineered virus. (No further information is provided.)

This is not the first time that unauthorized research involving smallpox genes has taken place. In 2005, Sandia National Laboratories in the US acquired at least two synthetic smallpox genes and expressed them in cell culture to produce variola proteins. The outcome of these experiments does not appear to have even been made public, however, there is no doubt that they did not comply with WHO rules. Sandia, a defense lab whose primary mission is to develop weapons, is part of the US Department of Energy. It has no public health mission. The World Health Assembly, in contrast, has prohibited variola

research that is not essential to public health and which does not address specific public health needs. Sandia's research was not to address essential public health questions.

Unnecessary Diagnostic Research Using Live Variola: Despite the fact that both the Major Review and the ACVVR have concluded that plenty of accurate and rapid smallpox diagnostics exist to meet public health needs, the ACVVR has decided to permit US researchers to develop still more diagnostic tests using live variola virus. A protocol approved last year allows use of the virus: "*Ultimately, live variola virus will be employed to define the utility of assays for detection of variola virus.*"

It is difficult to explain how this research was approved when WHO's experts have repeatedly concluded that new diagnostics are not essential. In fact, the ACVVR is one of the very committees that has concluded that further diagnostic development is not necessary, yet it paradoxically approved use of variola in development of new diagnostics. This lends further weight to the argument that WHO is not in control of variola, and that its expert committee has bowed to US pressure.

Another Failure of the Animal Model For many years now, work on an animal model of smallpox infection has been criticized because of risk of an accident and poor research results. Development of an animal model was authorized by WHA, but experiments over many years have not successfully induced monkeys to develop a disease that tracks the course of human smallpox, which is the main function of an animal model.

Instead, monkeys exposed to variola either do not develop smallpox disease at all or progress immediately to an advanced state of disease comparable to the end stages of human infection. This makes the model of very limited reliability for vaccine and drug testing, its intended purpose. With repeated animal studies showing little promise, few were surprised when the AGIES concluded in the Major Review that the effort should be shelved in favor of using other animal models that do not require variola virus, such as using monkeypox in monkeys – a more promising avenue of research that does not require variola.

Despite this, in 2010 the ACVVR permitted use of the animal model with live variola in order to test the efficacy of ST-246, a candidate smallpox antiviral drug. Unsurprisingly, the first such test was a failure. None of the monkeys – both control animals and those treated with ST-246 - developed smallpox. Data has yet to be released from a second attempt.

Remarkably, however, despite the AGIES Major Review recommendation to move away from animal studies with live variola, and the 2011 experiment failure, at the end of last year, the ACVVR's scientific subcommittee authorized still more animal model experiments with live variola virus in 2012, once again to try to test ST-246 efficacy.

As is the case with continued use of variola to develop redundant diagnostics, the ACVVR's approval of continued use of the variola animal model suggest that WHO's public health experts are being subverted by those opposing destruction of the virus stocks.

Conclusion

After the debate of 2011, smallpox will not be a substantive item on the Executive Board and World Health Assembly agenda in 2012. Nevertheless, the ACVVR's apparent inability to reign in new and redundant research projects, even at this late date, is a disturbing development that suggests that WHO is losing its grip over smallpox research. This matter should be raised in discussions among governments.

At the Executive Board and World Health Assembly, Member State will have the opportunity to comment upon the reports of the Secretariat and the ACVVR. In doing so, they should express concern at ACVVR actions that are inconsistent with the AGIES Major Review report and, indeed, with the ACVVR's own scientific conclusions. Member States should stress the need for WHO to be winding down research with variola virus in anticipation of 2014. Greater attention should be paid by Member States and WHO leadership to the operations of the ACVVR to ensure the Committee's integrity and that it fulfils its mandate to enforce WHA decisions to restrict research with live variola virus.