TWN
Third World Network
Website: www.twnside.org.sg
Address: rue de Lausanne 36, 1201 Geneva, Switzerland
Tel: + 41 22 908 35 50 **Fax:** + 41 22 908 35 51
Email: twngeneva@bluewin.ch

Briefing Paper

Smallpox Virus Stocks at the 64th WHA: Implementing the Conclusions of the Major Review[1]

Contents

Introduction	**2**
Background: Conflicts of Interests and A Review in Two Parts	**2**
Genome Sequencing and Diagnostics	**3**
Vaccines and the Animal Model	**4**
Antiviral Drugs	**6**
Synthetic Biology and Smallpox	**8**
US National Academies of Science Study	**9**
Concrete Steps at the 64th World Health Assembly	**9**
Dealing with Resistance to Fixing a New Destruction Date	**10**
Increasing Importance of Robust Oversight	**12**
Conclusion	**12**

[1] This paper was written by Edward Hammond, with contributions from Lim Li Ching.

Introduction

The 64th World Health Assembly (WHA), meeting in Geneva from May 16th 2011, will hold a major review of destruction of variola (smallpox) virus stocks. It will be the most important such discussion in recent years, as the WHA will consider a scientific and public health review of variola virus research from 1999 through 2010. The outcome of this review, which found no compelling public health reason to continue to retain the virus, provides the 64th WHA with clear justification to terminate research involving live variola virus and to schedule the prompt destruction of remaining variola virus stocks.

The United States (US) and Russia, who host the two World Health Organization (WHO) Repositories where the virus stocks are held, can be expected to resist. While the reasons for this resistance are largely political, they will attempt to cloak this fact with a thin, illusory veneer of science and public health arguments. These obfuscations, however, have been explicitly rejected by WHO's public health experts, who have reviewed the state of research involving live variola virus and found no essential public health purpose for which to retain the viruses.

Overcoming resistance from the US and Russia will be difficult, but by maintaining clarity of purpose, and differentiating between specious retention arguments and public health realities, in 2011 the Member States of the WHO are in the position to finally realize the multi-generational goal of truly eradicating smallpox.

Background: Conflicts of Interests and A Review in Two Parts

The major review of variola virus research at the 64th WHA is a result of the 60th WHA's Resolution 60.1. That resolution asked the Director-General to perform the major review so that the 64th WHA could arrive at consensus on the timing of destruction of the virus stocks.

The review is presented in two parts and there are important reasons why two documents are tabled. These relate to intrinsic conflicts of interest in oversight of WHO authorized variola virus research and WHO's attempt to convey them by presenting separate scientific and public health assessments.

For many years, the WHO's oversight of variola virus research was debilitated by improper influence from scientists with conflicts of interest and very poor representation of developing countries. Frequently, the very scientists that were conducting variola research (or from the same US and Russian institutions) were appointed by the WHO to be overseers of the research programme. This created a lax climate, in which the WHO regrettably failed to effectively oversee variola virus research.

The unacceptable situation of lack of independent and rigorous WHO oversight began to change following the 58th WHA, when the Assembly rejected a WHO committee's approval of genetic engineering experiments with smallpox. This controversy drew attention to how severely WHO supervision of variola virus research had been compromised.

Given the problems with conflicts of interest, preparing the major review for the 64th WHA presented a challenge for the WHO. The relatively few scientists who have recently worked with live variola virus are mostly employees of the Russian and US governments, which are politically resolved to retain the virus and seek to develop scientific justifications for their policy.

Thus, asking this group of variola researchers to opine on the value of retaining variola virus stocks can only result in arguments to retain the virus. It is like asking a group of restaurant owners if eating out is a good thing. Of course they will say yes – it benefits their business and person – whether they are serving a healthy meal or artery clogging trans-fats.

As experts in defense and orthopoxviruses, most of these variola scientists are limited in the perspectives they represent, and too often place alleged "national security" issues ahead of public health. Therefore, it was required (and it was emphasized by Member States) that the review includes broader public health perspectives and independent public health experts.

The major review is therefore divided into two parts: A scientific review paper (WHO/HSE/GAR/BDP/2010.3) and a public health assessment (WHO/HSE/GAR/BDP/2010.4).

The scientific review paper mainly represents the views of virologists who work with smallpox and related orthopoxviruses. Each of its chapters is authored or co-authored by US and/or Russian government scientists employed by the ministries that host the WHO Repositories. It presents an "inside view" from scientists at institutions committed to ongoing variola virus research, filtered through the WHO's Advisory Committee on Variola Virus Research (ACVVR).[2]

The public health review paper was prepared by the Advisory Group of Independent Experts to review the smallpox research program (AGIES). The AGIES paper offers a review of research undertaken (as documented in the scientific review paper) and an assessment of whether additional research using live variola virus is necessary from a global public health perspective.

This group of ten public health experts, appointed by the Director-General, did not include representatives of the WHO repositories in Russia and the US, or the respective ministries that manage them. It was also notably more geographically balanced than the scientific paper authorship, including experts from all WHO regions.

Thus, while the scientific review paper provides important data from persons working inside the smallpox field, mainly in the service of the US and Russian governments, the AGIES paper is the global public health review of variola virus research that the 60th WHA requested and that the 64th WHA should primarily rely on to inform its deliberations.

The AGIES concludes, as the following sections of this paper will relate, that no essential public health need now exists for live variola virus,[3] meaning that the WHA's purpose in authorizing temporary retention has been fulfilled. This provides unequivocal public health justification for the 64th WHA to set a prompt destruction date and finally rid humanity of the smallpox virus.

Genome Sequencing and Diagnostics

The need for live variola virus for genome sequencing and diagnostics has not existed for several years and no additional research with live virus for these purposes must be permitted.

Dozens of variola strains have been sequenced and this data has been published,[4] and even before the major review, the ACVVR "*repeatedly agreed that further sequencing was not justified for public health*."[5] Now, the conclusion of the AGIES is just as clear: "*the AGIES feels that there is no public health need for sequencing of additional variola virus isolates*."[6]

---

[2] The ACVVR acronym has recently come into WHO use and is used here. This is the same committee that has been referred to in previous Third World Network (and other) publications as the "VAC", for Variola Advisory Committee.
[3] As detailed in the following sections, the only ongoing use of variola virus that the AGIES found potentially justified related to antiviral research. But the AGIES concluded that this need could be promptly ended by an agreement between regulators and scientists. It thus presents no obstacle to destroying the remaining virus stocks.
[4] WHO (2010). Scientific review of variola virus research, 1999-2010. WHO/HSE/GAR/BDP/2010.3. pp. 47-48.
[5] WHO (2009). WHO Advisory Committee on Variola Virus Research: Report of the Eleventh Meeting. WHO/HSE/GAR/2009.3, p.2.
[6] WHO (2010). Advisory Group of Independent Experts to review the smallpox research programme (AGIES). Comments on the *Scientific Review of Variola Virus Research, 1999-2010*. WHO/HSE/GAR/BDP/2010.4, p.5.

→ **Further debate about sequencing is unnecessary. No further sequencing should be authorized, and the WHA should immediately withdraw its authorization for retention of variola stocks for this purpose.**

Similarly, rapid, modern, and accurate diagnostics exist for variola and have existed for years. These diagnostics distinguish variola from other orthopoxviruses and can detect as few as 20 virions in a sample. An arguably non-essential test even exists that can distinguish between *Variola major* (smallpox) and *Variola minor* (alastrim).[7]

The ACVVR has concluded that these tests may be widely used: "*Publications have described the probes and other information in sufficient detail to be replicated in other laboratories*."[8] and the WHO is moving to create a network of laboratories equipped and practiced to perform these diagnostics as required.

Thus, the conclusion of the major review is: "*The AGIES is of the view that live variola virus is not required for the further development of diagnostic tests nor for technical assay validation*."[9]

→ **Accurate, rapid, and validated diagnostics exist for smallpox. Variola virus is neither needed to maintain these tests nor a global laboratory network capable of using them. Further discussion of this issue is not needed. The WHA should immediately withdraw authorization for retention of variola stocks for the purpose of diagnostics.**

Vaccines and the Animal Model

For years, US Department of Defense-linked scientists have attempted to create variola infections in monkeys that mimic human smallpox. The purpose of these dangerous studies has been to develop an animal model for use in vaccine and antiviral research.

In these experiments, monkeys were generally asymptomatic at low doses of virus. Unable to provoke smallpox cases in monkeys with "normal" doses of pathogen, the American researchers finally got the monkeys to manifest the disease by inoculating them with huge doses of variola. These monkeys immediately progressed to advanced illness and died or were euthanized. They did not display disease corresponding to the early stages of human infection, severely limiting their usefulness as a model of human infection. Despite repeated experiments, primates (and other mammals) simply have not been induced to develop disease with strong parallels to the course of human infection.

With respect to vaccines (antivirals are addressed later in this paper), existing vaccines such as Dryvax were the tools that eradicated smallpox in the first place. Smallpox vaccines use various strains of vaccinia virus, and do not contain variola virus or need variola virus for manufacture.

In recent years, second and third generation smallpox vaccines with fewer contraindications have been developed. Some of these have obtained regulatory approval, and others are well advanced in the process of doing so. It is thus beyond question that multiple effective smallpox vaccines exist, including newer vaccines with enhanced safety profiles.

---

[7] WHO (2008). WHO Advisory Committee on Variola Virus Research: Report of the Tenth Meeting. WHO/HSE/EPR/2008.9, p. 3. The test is arguably non-essential because the response and treatment regime for smallpox or alastrim would be largely identical.

[8] WHO/HSE/EPR/2008.9, p. 3

[9] WHO/HSE/GAR/BDP/2010.4, p. 6.

It has therefore been clear for a number of years that the WHA's reason for permitting temporary retention of virus stocks has been satisfied with respect to vaccines and that no compelling public health reason exists to retain variola virus for vaccine purposes.

Unable to justify continued retention of variola virus for vaccine research and development, the US has turned to justifying retention on the basis of its potential domestic regulatory requirements for future vaccine licensure. The US argues that approval of new smallpox vaccines (and antivirals) requires demonstration of their efficacy using live variola *because the rules of its regulatory agency say so*. Therefore, the US argues, the WHA should defer to US regulators.

If the logic of this US argument were to be accepted, and the WHA was to devolve its prerogative to an agency of the US government, then variola virus would likely never be destroyed because its use would always be possibly required for regulatory activities related to vaccines (or drugs).

In reality, the argument that variola virus must be retained for regulatory purposes is little more than a straw man for the US political purpose of retention. US researchers and regulators are perfectly capable of developing alternatives methods for vaccine (and drug) approval purposes. They choose not to take this logical course of action, however, because doing so would undermine the US retention policy, which is motivated by geopolitical concerns.

The AGIES panel has underscored this reality by drawing the strongest conclusion yet in a WHO publication that animal model studies are dangerous and that the American regulatory approval argument is flawed. The AGIES concludes that variola virus is no longer needed for vaccine research because of the dangers the research poses and because alternative animal models utilizing related orthopoxviruses may be used for research and regulatory purposes:[10]

> "*From a public health perspective, the risks associated with the use of live* [variola virus] *for* in vivo *animal studies on vaccines outweigh the benefits of these animal models over the models that rely on other orthopoxviruses… researchers in the field and regulatory authorities should urgently discuss, and jointly arrive at a consensus on, acceptable* ***surrogate markers*** *of protection and the most appropriate* ***surrogate model(s)*** *for testing vaccines against variola virus infection*."

→ **The AGIES public health review concludes that animal model research involving live variola virus is not worth the risks it poses and that research should instead focus on improving surrogate models that use other orthopoxviruses. No further animal model research using variola should be authorized and the WHA should withdraw its authorization for retention of variola virus for the purpose of an animal model.**

→ **The AGIES public health review concludes that live variola virus is no longer necessary for vaccine research and development. Vaccine research may continue; but in studies not involving use of live variola virus. No further vaccine studies involving variola virus should be authorized and the WHA should withdraw its authorization for retention of variola virus for the purpose of vaccines.**

→ **The AGIES public health review expressly rejects the argument that live variola virus is necessary for regulatory approval of smallpox vaccines. Smallpox vaccines that have not already received regulatory approval may be reviewed using alternative models and markers of protection.**

---

[10] WHO/HSE/GAR/BDP/2010.4, p. 29 (emphasis added).

Antiviral Drugs

The WHA has authorized retention of variola virus stocks for essential public health research for the development of new antiviral drugs. It is generally understood that this means the availability of two different compounds to treat variola virus infections. Presently there are two primary drug candidates for treatment of smallpox infection – ST-246 and CMX001, proprietary compounds owned by the US pharmaceutical companies Siga and Chimerix, respectively.[11] Both have demonstrated effectiveness in a variety of experiments.

In assessing antiviral drug research with live variola virus and its risks, it should first be recalled that the primary public health response to variola virus infection, should it ever reappear, would be vaccination. In addition, at least some smallpox vaccines (e.g. Dryvax) can be used post-exposure to prevent or lessen the severity of smallpox disease.

Antiviral drugs are thus a supplement to and are not the core of any public health response to a smallpox outbreak, should one ever occur. Specifically, antiviral drugs have a limited role, in that they are used to treat only those persons exposed to variola virus before vaccines are deployed.

Both candidate smallpox drugs are now being assessed for their safety in humans. To date, ST-246 has a high safety profile, and CMX001 – an analog of an already licensed drug – shows no evidence of the nephrotoxicity of its progenitor (when used in high doses). As such, there are strong indications that both drugs will prove safe to administer. The AGIES thus concludes, "*the research programme on drug development may be close to reaching its overall objectives – probably even closer than suggested by* [the scientific review paper]".[12]

The situation with antiviral drugs therefore resembles that with vaccines. With little justification for virus retention for the purposes of drug development (because two advanced drug candidates already exist), proponents of virus retention have fallen back to basing their arguments on regulatory requirements.

The specific claim with respect to antiviral drugs is that because there are no human cases of smallpox to study, the candidate antivirals cannot be licensed without demonstration of their efficacy in an animal model utilizing live variola virus that the regulators deem to sufficiently reflect human smallpox disease.

As previously discussed, however, no such animal model with variola virus exists, and efforts to develop one have failed. As we and others have argued for years, from a public health perspective the risks of further animal model research outweigh the potential benefits and alternative animal models not using variola virus are more promising for evaluation and for obtaining regulatory approval of smallpox drugs.

WHO's own studies now also reflect this opinion (previously also voiced by members of the ACVVR). The AGIES conclusion in this regards bears emphasis:[13]

> "*Although current non-human primate models using* [variola virus] *are suboptimal, the amount of research conducted into developing them further, and success at achieving this goal over the last decade, has been rather limited. The only reason for attempting to develop such a model is to meet the current stringent regulatory requirements, in the absence of human variola virus infection. The AGIES's opinion was that a more*

[11] CMX001 is an analog of a third compound, cidofovir, which is licensed for other antiviral uses and itself has demonstrated activity against variola virus. CMX001 appears to have fewer side-effects than cidofovir itself.
[12] WHO/HSE/GAR/BDP/2010.4, p 26.
[13] WHO/HSE/GAR/BDP/2010.4, p. 30.

productive approach would be for the regulatory requirements for vaccine and drug approval for variola virus infection to be reconsidered, given that human infection with the virus no longer occurs."

So, whereas the US says that the WHA should defer to the unilateral policies of the US Food and Drug Administration (which itself is a hostage of US geopolitical interests), the WHO's public heath assessment says that the FDA's policies should be changed.

Having concluded that the ultimate route to licensure for antiviral drugs is through models not involving live variola virus, the AGIES does suggest in its report that in the interim before alternative models are agreed upon, that *in vitro* use of variola virus "appears reasonable", but that such research could be accomplished with a limited number of strains.[14]

The AGIES do not suggest a timeline for coming to an agreement on alternative models and markers. We suggest that this can and should be quickly accomplished, within months. Moreover, agreement on alternative models is not a prerequisite to preparing for destruction of virus stocks. This agreement can be developed in parallel with preparations to destroy smallpox stocks by a date fixed by the 64th WHA.

On its own, the AGIES conclusion that antiviral (and vaccine) regulatory approval should be accomplished without use of live variola virus is sufficient for the WHA to withdraw its approval for retention of variola virus for these purposes.

Additional information supporting this decision can also be considered:

First, the US FDA's "Animal Rule" applicable to regulatory approval of new smallpox drugs[15] does not require that animal studies utilize the pathogen that the drug seeks to counteract in humans. Rather, the regulation states that when it is impossible or unethical to conduct new drug studies on humans, well-controlled studies with animal models must "*establish that the drug product is reasonably likely to produce clinical benefit in humans*".[16] There is no requirement to use variola virus, and studies need not show effectiveness against actual variola virus in primates, rather, regulators may use alternative animal models to demonstrate a *reasonably likely* benefit.

Finally, it may be questioned if regulatory approval of smallpox drugs is necessary at all. The difficulty in obtaining approval for smallpox drugs relates to the fact that there are no human cases in which to study the disease and its treatment. There are, however, related human conditions involving similar pathogens that continue to occur and upon which more modern science has been conducted, facilitating the development of animal models. These include monkeypox infection in humans and eczema vaccinatum, or disseminated infection with vaccinia virus, which occasionally occurs in lab workers, persons vaccinated against smallpox, and persons coming into contact with the former groups.

Given the unique characteristics of smallpox as an eradicated disease, it may be reasonable to license ST-246 and/or CMX001 for treatment of vaccinia and/or monkeypox, and then rely upon their use under emergency permit in the extraordinary event of an outbreak of smallpox. Indeed, the US has already allowed use of the unlicensed ST-246 and CMX001 in a case of eczema vaccinatum.

---

[14] *In vitro* work would preclude further animal studies, restricting live variola to experiments in laboratory vessels.
[15] The US regulation is 21 CFR 314.600. It may be viewed at URL: http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/cfrsearch.cfm?cfrpart=314&showfr=1&subpartnode=21:5.0.1.1.4.9
[16] US Code of Federal Regulations: 21 CFR 314.610(a).

→ **The US argument for retention of variola virus for drug development is based on an alleged need to develop animal models in order to obtain regulatory approvals. The AGIES public health review rejects further animal model research as too dangerous and unpromising, and instead calls for use of alternative models and markers to achieve regulatory approval. The AGIES notes that while these alternative models and markers are agreed upon, *in vitro* use of variola virus "appears reasonable".**

The regulatory straw man cannot interfere with the WHA's commitment to destroy the virus stocks. Accordingly, the WHA should set a specific and irrevocable destruction date in the near future. In the short interim before that date, alternative regulatory procedures must be agreed upon, and only *in vitro* use of limited strains of variola virus that serves an essential public health purpose related to drug development (if any) may be authorized and conducted. This research must be terminated by the destruction date and, in any event, must not be allowed to interfere with it.

Synthetic Biology and Smallpox

WHO's review of smallpox research rightly raises issues with respect to the increasing scientific ability to synthesize long stretches of nucleic acids up to and including viruses and bacteria. Smallpox itself has not been synthesized and doing so remains a great technical challenge. While the issue merits consideration, the 64th WHA's consideration of smallpox stock destruction should be focused and it is not the proper time and place for a detailed discussion of synthetic biology risks.

Firstly, it should be recognized that the issues raised by synthetic biology are not unique to smallpox, in the sense that online sequence data and developing gene synthesis technology theoretically enable synthesis of other tightly controlled pathogens that pose a public health threat, such as 1918 influenza (itself recreated by synthesis) and Ebola virus.

What is unique about smallpox, however, is the WHA's control over the virus, the fact that it is restricted to two authorized repositories, and that existing rules restrict other labs from possessing more than 20% of the virus genome.

The issue that underlies the questions that have been raised about synthetic biology and smallpox is "*What happens if a misbehaving scientist or institution recreates the smallpox virus through synthetic biology or related techniques*?" After all, it is impossible for authorities to be looking over the shoulder of every lab, and every lab technician, all the time, even though it should be remembered that the scientific challenges in recreating smallpox are, and will remain in the near future, such that few labs in the world would have a strong chance of overcoming them.

The most powerful statement that the WHA could make that synthesis of smallpox is prohibited would be to destroy the remaining virus stocks. So long as permitted virus stocks remain, some ambiguity about possession of the virus will continue to exist. If the WHA sees through destruction of the stocks, however, possession of smallpox virus (natural or synthesized) will become a completely unambiguous crime against humanity.

After destruction of the stocks and criminalization of virus possession, the WHA can take additional steps to prevent unauthorized possession of synthetic variola virus and variola DNA. While smallpox will always be a case of special and heightened concern, these steps should be taken in harmony with a broader WHO effort to address the risks associated with synthetic biology and pathogens of high public health consequence.

→ **At the 64th WHA, Member States should note the need to address the risks related to variola virus and synthetic biology and commit to doing so. The first and most important step that WHA can take, however, would be coming to consensus on the timing of the**

destruction of virus stocks and criminalization of virus possession. The WHA should commit to addressing variola synthetic biology risks in harmony with an approach addressing the synthetic biology risks associated with other pathogens of high public health consequence. The 64th WHA should not, however, permit synthetic biology issues to distract it from the primary task of fixing a prompt destruction date. Indeed, fixing such a date is the critical first step to addressing synthetic biology risks.

US National Academies of Science Study

Prior to the WHO major review, the US government asked a committee of its National Academy of Sciences (NAS) (through the US Institute of Medicine) to study uses of variola virus. This committee's report, published in 2009, appears to make a number of arguments for retention of variola virus and may be cited by the US or others.

The conclusions of this paper, however, cannot be validly applied to the WHA's debate. That is because the US NAS committee was specifically instructed not to consider the benefits of virus destruction and not to consider the risks of virus retention. At the outset of the committee's meetings, it was told by the US government that "*Now the debate and discussion on destruction versus retention: First, that is not the job of this committee."* Further, the committee was not instructed to consider the role of the WHA and the WHO in its deliberations.

As a result, the NAS study was not an exercise in determining if further research with variola virus research is essential for public health. Instead, it was an exercise in speculating about what US scientists might want to do with variola, if it were to be retained forever, if WHO Member States are ignored, and if WHA resolutions did not apply to the research.

This approach, ungrounded in reality, resulted in ideas very inconsistent with WHA resolutions and essential public health needs. These include an argument that variola stocks should be retained for general human immunology research with no relationship to public health response to variola, and the view that there is no time-limited endpoint to vaccine and antiviral research. Due to its instructions to avoid the issues of virus destruction and retention risks, the NAS committee presumed that vaccine and antiviral activities with live variola would be desirable to permit in perpetuity.

That is, it is easy to argue that almost any health product might be improved by further research, but it does not follow that such improvements, if in fact possible, are worth their risks or essential to public health. The application of this balance and good judgment is what the NAS Committee was specifically instructed to ignore.

For a more detailed discussion of the NAS report, please refer to Third World Network's 2010 *Update on Smallpox (Variola) Virus Destruction* (Briefing Paper #1 for the 63rd WHA), pages 8-12.

Concrete Steps at the 64th World Health Assembly

Noting reports or calling for destruction, in and of itself, will not have the effect of making it happen. Existing WHA decisions, permitting continued temporary retention, would remain the formal legal decision of the WHA. Thus, the 64th WHA must resolve to bring about the destruction of variola virus by adopting a resolution that explicitly does the following:

1. The WHA must withdraw its authorization for continued temporary retention of variola virus stocks for research purposes that have been satisfied (or, in the case of the animal model, explored and deemed unproductive). To do this, operational language of a WHA

resolution must explicitly withdraw authorization for continued temporary retention for the purposes of sequencing, diagnostics, animal model, vaccines, and antiviral drugs[17]. These withdrawals will ensure that no new research is begun and will eliminate legal justification for retention.

2. The WHA must set a destruction date for the virus. It is suggested that this date be fixed immediately before the 65th WHA or at the outside, the 66th WHA. History has shown that despite previous destruction dates set by WHA, the US and Russia have resisted. It is therefore important that the resolution include very strong language with respect to the requirement that the repositories destroy their virus stocks.

Dealing with Resistance to Fixing a New Destruction Date

It is certain that the US and Russia will resist fixing a new date for destruction of virus stocks. Their reasons relate to the legacy of Cold War rivalries and undocumented and unproven fears (with no evidence) that secret stocks of smallpox virus are held by "rogue states" or terrorists.[18] Although the US and Russia have no greater claim to much of the virus material in the WHO Repositories than many other Member States, the two countries have come to view themselves as somehow exceptional.

Science and history, however, are squarely on the side of variola virus destruction. The AGIES could find no public health justification for continued virus retention – even regulatory approval concerns, the AGIES ultimately concluded, can be resolved with alternatives to live variola virus. Through the lens of history, a decision at the 64th WHA to finally destroy the virus stocks will represent the successful culmination of what is arguably the WHO's greatest achievement – eliminating the scourge of variola.

The US and Russia do not wish to admit that they seek to retain the virus for reasons not related to public health. Therefore, foremost, countering American and Russian resistance will be a matter of rejecting disingenuous and obfuscating scientific arguments that the US and Russia will advance.

For example, the US is likely to cite a 2009 study that the Institute of Medicine of its National Academies of Science conducted. This study suggested various future uses of variola. What the US is less likely to mention, however, is that the study panel was prohibited from considering the destruction of variola. Instead, it was solely instructed to speculate on what scientists might like to do with variola virus if it were to be kept forever, without regard to WHA resolutions, public health cost-benefit considerations, or even pondering the risk of virus escape.

Similarly, the US and Russia may selectively cite portions of the WHO scientific review (WHO/HSE/GAR/BDP/2010.3), written by their own government scientists, to support a case for virus retention. In assessing these arguments, however, careful attention should be paid to the complete report language and great care should be applied to making the appropriate balances.

For example, consider the scientific review on animal models: This section of the review, written by an American defense researcher, is laced with the mindset and terminology of military and security

---

[17] As discussed previously, for antiviral drugs, a limited, time-bound exception for *in vitro* use may be considered in the interim before alternative models are agreed for regulatory purposes; but, in any event, no such research should be permitted to interfere with implementation of the destruction date.

[18] One does not need to have variola virus in storage, however, to respond to an attack with variola virus. The health response to such an attack would rely on vaccines made from vaccinia virus. And if variola is released into the wild by a terrorist or "rogue state", it will obviously again become available for collection and study by governments. Indeed, the only foreseeable significant immediate use of pre-existing variola virus stocks in response to a terrorist attack with variola virus would be to retaliate in kind, in violation of international law.

policy ("countermeasures", "bioterrorists", "select agent" etc.[19]) rather than the language of public health. In it, a weak argument is presented for retaining variola virus for animal experiments. This argument is that continuing to use variola virus would provide "*increased confidence in countermeasures*".[20] "*Increased confidence in countermeasures*", however, does not satisfy the WHA's criterion that variola research be essential for public health. Proponents of virus retention may ignore this critical difference.

Similar obfuscation is possible with antiviral research, a section of the scientific review written by US and Russian defense researchers. In this section, another weak argument for retention of variola virus is presented. The review repeatedly states that it "*could be argued*" that variola virus is necessary for further drug discovery work.[21] The review does not actually claim that it is essential for public health, instead, it merely states that it "*could be argued*". The only subject on which the scientific review expresses certainty of the need of variola virus relates to obtaining regulatory approval[22] – an argument which, as previously discussed, was explicitly rejected by AGIES.

Thus, although proponents of virus retention have very little science to rely upon, even in the Scientific Review written by their own scientists, it can be expected that distorted arguments will be many. These must be rejected by careful review of the documents and by maintaining clarity about WHA's purpose.

There are also options available to Member States to place pressure back on the US and Russia:

Firstly, scholarly research has raised the question that if US and Russian resistance is so entrenched, it will require a vote of the WHA to fix a destruction date.[23] A vote would be unusual at the WHA, however the Rules of Procedure for the WHA set forth the manner for conducting one. Past positions of Member States suggest that sufficient support for prompt virus destruction exists such that a date may be set through a resolution adopted by voting. Whether or not a vote takes place at the 64th WHA, the prospect of a vote will place pressure on the US and Russia. Simply raising the possibility at the 64th WHA will establish a precedent that will facilitate voting, if it becomes necessary at future meetings.

Secondly, the US and Russia can be invited to confront the ramifications of their argument that they must, in effect, indefinitely retain smallpox virus for defense purposes. The viruses that comprise the WHO Repositories were collected in many countries, primarily developing countries, and were transferred to the WHO following the eradication of smallpox in the wild. These viruses do not belong to Russia and the US. They are held by the WHO on behalf of the countries where they were collected and that deposited them.

The US and Russia have argued that these viruses are needed for biological defense purposes, however, the US and Russia are not the only two countries that may need to defend themselves against so-called "rogue states" or alleged "bioterrorists". Other countries also may need to protect themselves against possible use of disease as a weapon, and if smallpox must be retained by the US and Russia to defend themselves, as they argue, it would be logical that other countries with biological defense needs might argue that they too need to possess variola stocks.

Of course the objective upon which the world agrees is to destroy all virus stocks, and variola outbreaks can be controlled by existing technologies. American and Russian exceptionalism,

---

[19] WHO/HSE/GAR/BDP/2010.3, pp. 86-87.
[20] Ibid, p. 87.
[21] WHO/HSE/GAR/BDP/2010.3, p. 105 and p. 121.
[22] Ibid, p. 121.
[23] Tucker JB (in press). Breaking the Deadlock Over Destruction of the Smallpox Virus Stocks. Biosecurity and Bioterrorism. doi:10.1089/bsp.2010.0065

however, has enabled those countries to illogically argue for special privilege. Yet the Cold War adversaries have no greater claim to many of the virus stocks than dozens of other WHO Member States, many of whom have the capability to host a WHO Repository.

Ultimately, it is undesirable for variola virus stocks to be distributed to any new location, as this would only present new risks and complicate their destruction. The nature of US and Russian exceptionalism, however, may induce other WHO Member States to inform the US and Russia that if they continue to resist destruction of virus stocks, then the logical conclusion is that other countries might seek their own stocks for their own defense purposes. The prospect of WHO Repositories in other countries may cause the US and Russia to rethink their positions.

Increasing Importance of Robust Oversight

As the number of WHO-authorized experiments with live variola virus dwindles, Member States should pay special attention to the activities of the ACVVR, which is the WHO committee that directly reviews and oversees variola virus research. The ACVVR's actions will be even more important to monitor if the 64th WHA withdraws authorization for virus retention for research purposes that have been satisfied (or, in the case of the animal model, proven unproductive).

In the past, the ACVVR has come under criticism by non-governmental organizations and Member States for being inappropriately influenced by Russia and the US. As a result of these criticisms, WHO has improved the operations of the ACVVR in recent years through better geographic balance, more systematic procedures, and increased transparency. Nevertheless, there remain a number of concerns about this committee, whose actions will be critical to ensuring implementation of a decision to destroy virus stocks.

First, conflicts of interests continue to exist, and the disagreements that these conflicts have generated are apparent in the ACVVR's reports. Full members of the committee are employed by the Russian and US ministries that operate the WHO Repositories. Also, while greater geographic balance has been achieved, developing country members have not attended as consistently as others, and the committee's meetings (which are by invitation only) continue to be overloaded with Northern "advisors", many of whom have personal or institutional interests in variola virus research.

Thus, the 64th WHA should direct the Director-General to instruct the ACCVR to ensure that already authorized research is promptly concluded so as not to interfere with preparations for virus destruction. The WHA should also ask the Director-General to instruct the ACVVR not to approve any new protocols for types of research whose goals have been satisfied (or which have proven unproductive).

Conclusion

Historians may eventually debate if the last several years of continued temporary retention of variola virus stocks were scientifically valid or merely the result of delaying tactics by the US and Russia. What is clear now, however, is that the scientific arguments for virus retention are fully played out – both in the estimation of WHO's public health experts and in that of the vast majority of independent scientific experts, including the dwindling number of surviving experts from the smallpox eradication program:

> *It is a twist of irony that the United States and Russia, the two nations that jointly sponsored the WHO resolution to eradicate smallpox, are now the main proponents of maintaining live stocks of the virus. The advocates of retention of the virus have*

research goals that are only remotely accomplishable and, we believe, unnecessary given our current scientific understandings.[24]

Thus conclude, in an early 2011 editorial, the Editor-in-Chief of *Vaccine*, and the former Director (1973-1981) of the US Centers for Disease Control Smallpox Eradication Program.

For well over a decade, the US and Russia have resisted calls to destroy the remaining variola virus stocks, and this position is unlikely to have changed at the outset of the 64th WHA. What is different in 2011, however, is that as a result of the major review set into motion by the 60th WHA, public health arguments for continued virus retention are completely exhausted. In the estimation of WHO's public health experts, the only remaining scientific arguments for retaining the virus - for animal model and regulatory-related research - are invalid because non-variola surrogate models can be used.

Overcoming the political opposition of the Cold War rivals, now united in an awkward embrace, is a significant but final hurdle in the process of culminating the eradication of smallpox. It is a difficult task that must be done for the sake of past sacrifices and future generations' health. By fixing a destruction date in the next one to two years and formally withdrawing its authorization for continued temporary retention for any research purpose, the 64th WHA can reclaim the lost mantle of the successful 1960s and 1970s WHO eradication effort, and set in motion the final chapter of humanity's victory over this most dreadful disease.

[24] Lane JM & GA Poland (in press). Why not destroy the remaining smallpox virus stocks? Vaccine (2011), doi:10.1016/j.vaccine.2011.02.081