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 1

63rd WORLD HEALTH ASSEMBLY

17 to 21 May 2010, Geneva, Switzerland

Update on Smallpox (Variola) Virus Destruction[1]

Contents

TWN THIRD WORLD NETWORK is a network of groups and individuals involved in bringing about a greater articulation of the needs, aspirations and rights of the people in the Third World and in promoting a fair distribution of world resources and forms of development which are humane and are in harmony with nature.

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

Introduction

Since 2005, the World Health Assembly (WHA) debate on destruction of variola virus stocks has taken on new urgency and political importance. In that year, governments responded with grave concern to US plans to genetically engineer the extremely dangerous virus, which is eradicated from nature and solely exists at World Health Organization (WHO) Repository Laboratories in the United States and Russia.

The 2005 controversy prompted reversal of WHO approval for genetic engineering experiments including insertion of smallpox genes into other poxviruses and led to governments paying closer attention to the WHO's weak oversight of smallpox research. This culminated in 2007, in a WHA resolution that states that any research undertaken should not involve genetic engineering of the variola virus. This includes genetic engineering of the smallpox virus itself, and of other viruses with smallpox genes.

Nonetheless, dangerous research involving smallpox virus has continued, despite repeated (and unimplemented) WHA resolutions that the virus should be destroyed and the WHA's restriction that any research conducted before virus destruction be time-limited and only for WHA-approved essential public health purposes.

By resolution of the 55th WHA in 1996, the virus was originally to be destroyed in 1999; but to date Russia and the United States have refused to do so, resulting in subsequent WHA resolutions authorizing "temporary retention" of the virus until a new destruction date is set.

With pressure again mounting on the two countries for prompt destruction of the virus stocks, the US convened a committee of its Institute of Medicine[2] to elaborate on alleged future needs for live variola virus, a move it intended to provide a scientific rationale for its policy of virus retention.

In parallel and with the purpose of fixing a new date for virus destruction, the World Health Organization is currently conducting a "major review" of variola virus research for presentation to the Sixty-fourth World Health Assembly in 2011, when variola virus destruction will be a substantive agenda item. This review and the planned WHA discussion is pursuant to WHA Resolution 60.1 (2007), which strongly reaffirmed the decisions by previous Assemblies that the virus should be destroyed.

This paper provides an update on ongoing variola virus research projects, the WHO Advisory Committee on Variola Virus Research (VAC, for Variola Advisory Committee), and the US Institute of Medicine (IOM) committee. It makes recommendations for government actions aimed to ensure the destruction of smallpox virus at the earliest possible date.

Ongoing Research Involving Variola Virus

By WHA decision, all research involving live variola virus in the interim before its destruction must be approved by WHO and be under its control. It must also be time-limited, outcome-oriented, and reviewed by WHO. Perhaps most importantly for the present debate, all research must also be essential for public health, a requirement that prohibits research motivated by other reasons, such as academic concerns, intellectual curiosity, theoretical interests, or vague "future needs".

WHA has authorized research in the areas of: virus sequencing and diagnostic development, vaccine development and testing, antiviral drug development and testing, and development of an animal model of human smallpox disease. Not all research in the above areas is permitted, however, because

[2] Part of the US National Academies of Science.

in addition to falling into one of the above categories, the research must also meet the criterion of being essential for public health.

The state of research and VAC oversight in each of these areas is discussed in the following sections.

***Virus Sequencing*:** The VAC has "*repeatedly agreed that further sequencing was not justified for public health*."[3] Indeed, many times more smallpox strains have been sequenced than is necessary. The WHA should quickly move to formally withdraw approval for sequencing of variola virus stocks, by formal conclusion in a resolution, thereby closing one pretext that might be used in the future to justify continued retention of virus stocks.

The sequence of a representative strain or perhaps handful of strains is what is arguably was necessary for public health, in order to enable reliable and rapid diagnostics that differentiate variola from other orthopoxviruses. This goal was accomplished more than a decade ago and hence further sequencing is not necessary; there are enough data available for public health purposes. Yet Russia and the US have continued to sequence different strains of the virus. The sequences of 49 strains have been published so far, showing the diverse origin of these WHO Repository strains:[4]

COUNTRY	**NUMBER OF STRAINS** (of those with a published sequence)
Afghanistan	1
Bangladesh	5
Benin	1
Botswana	2
Brazil	1
China	1
Congo (Kinshasa)	2
Ethiopia	2
Germany	1
Guinea	1
India	5
Indonesia	2
Iran	1
Japan	3
Korea	1
Kuwait	1
Nepal	1
Niger	1
Pakistan	1
Serbia	1
Sierra Leone	1
Somalia	3
South Africa	2
Syria	1
Tanzania	1
United Kingdom	4

[3] WHO (2009). WHO Advisory Committee on Variola Virus Research: Report of the Eleventh Meeting. WHO/HSE/GAR/2009.3, p.2.

[4] See: http://www.poxvirus.org

The United States and Russia may continue to quietly sequence smallpox strains, perhaps utilizing DNA and other non-viable materials found in the WHO Repositories.[5] Indeed, the US National Academies have recently called for more variola sequencing (see below) for non-essential research.

WHA has missed previous opportunities to close the door on further sequencing. **Without prejudice to the most important objective of setting and implementing a destruction date, WHA can and should withdraw its authorization for the retention of variola stocks for the purpose of sequencing.** With WHO's own committee having repeatedly concluded that more sequencing is not necessary, there is ample justification for this step and, indeed, failure to do so might send the signal that WHO Member States are flagging in their determination, so long delayed, to destroy the virus stocks.

Diagnostics: Rapid, modern, and accurate diagnostics exist for variola and have existed for years. These PCR-based diagnostics distinguish variola from other orthopox viruses 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).[6] The VAC 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*."[7]

With multiple effective DNA-based assays available, the United States has unsurprisingly begun to argue that these are not enough. The US says a new protein-based test is necessary, and hence that retention of the live virus is needed for this purpose. These "strip tests", if developed, could theoretically be used by primary care personnel, providing a near-immediate indication of smallpox infection, rather than sending a sample to the lab. Arguing for protein-based tests, the US also confusingly conflates monkeypox outbreaks in Central Africa with smallpox testing.

In reality, such strip tests are not needed and a variola-specific diagnostic is not essential for control of monkeypox epidemics. First, the strip tests developed by the US currently do not work and US researchers have, for the past two years, failed to table a new proposal to use variola virus in further development. Second, while the notion of a smallpox strip test at point-of-care facilities sounds interesting, it is extremely unlikely that the vast majority of primary care facilities, especially in developing countries, would have the budget and supply chain to stock diagnostics for a disease not seen in any patient on earth for three decades. Even if a strip test was available, it cannot be assumed that primary care personnel that have never seen a smallpox case would use it, especially at early stages of infection.

Finally, the US suggests that a variola strip test is useful in Africa to rule out smallpox in human cases of monkeypox (which can manifest similar symptoms). Ruling out smallpox, however, can be accomplished by current PCR-based tests and by a monkeypox-specific strip test, meaning that the (hypothetical) variola specific strip test has no essential use in monkeypox outbreaks.

In fact, the only likely heavy users of a variola strip test would be the field operations of the US and perhaps some other militaries, such as that of Israel, who routinely scan for and vaccinate against very uncommon diseases (e.g. anthrax, smallpox) due to perceived biological weapons threats. Even in these cases, a positive strip test would certainly be sent for more definitive PCR confirmation before any conclusions were drawn.

---

[5] In addition to the live variola strains of most concern, the WHO Repositories include other materials that contain smallpox DNA, for example, scabs from smallpox victims, and samples frozen many years ago that did not yield living virus when removed from freezers.

[6] 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.

[7] ibid

For public health purposes, given the existence of accessible and reliable DNA-based diagnostics, what is essential is for WHO to proceed with the development of a global network of laboratories that is capable and practiced in smallpox diagnostic testing. This network can be created and maintained without need for variola virus.

Development of protein-based diagnostics is not essential for public health and is a false pretense for retention of variola virus stocks. The majority of VAC members have long held the view that no additional research involving the use of live variola virus is required for diagnostic purposes. **Because the WHA mandate for development of rapid and accurate diagnostics has been satisfied, the WHA should now formally withdraw authorization for the retention of variola virus for this purpose.**

Vaccines: Smallpox vaccination was discovered in the late 18th Century, and effective vaccines standardized by the 1960s were what enabled eradication of variola from the natural environment. A variety of effective vaccines exist, including newer vaccines with safety profiles improved from those most frequently used in the WHO eradication program.

Available vaccines include at least three vaccines used in the WHO eradication program, as well as new licensed and late-stage (not requiring variola virus[8]) "second" and "third" generation vaccines. Most recently, in March 2010, a new Danish-made vaccine based on the MVA strain of vaccinia received US regulatory approval. This vaccine, along with a Japanese vaccine licensed since 1975 (and safely used in more than 100,000 Japanese children), and a vaccine from Sanofi-Pasteur, all use attenuated vaccinia strains with improved safety for persons for whom older vaccines are contraindicated. In addition, new and safer manufacturing processes have been licensed for producing vaccine from older unattenuated vaccinia strains.

Simply put, not only do the vaccines that passed the ultimate test by eradicating smallpox in the first place still exist; but a number of additional vaccines with fewer side effects are approved or are in late stages of approval. None of these require variola virus and there is thus no longer any need for vaccine testing utilizing variola virus.

WHO and governments around the world have confidence in the effectiveness of these proven vaccines and WHO has stockpiled 32.620 million doses (and received pledges of 27 million more) for use in an emergency.[9] Of note, at least one of these vaccines (Dryvax) can be administered up to a week after exposure to variola and prevent or lessen the severity of smallpox disease.[10]

These simple and straightforward facts amply prove there is no reason for continued use of variola virus stocks for vaccine development and, as in the case with diagnostics and sequencing, the WHA should rapidly withdraw its authorization for retention of variola virus for this purpose.

Opponents of variola destruction have recently begun to argue that variola virus might be required for new vaccines that do not manifest a take (i.e. show inflammation at the point of inoculation, indicating successful vaccination). But such vaccines are not essential because a variety of proven and effective vaccines already exist. The WHA authorization was not to retain variola for attempted vaccine development forever.

---

[8] It should be recalled that smallpox vaccines use vaccinia virus. Variola virus is not (and has never been) needed for smallpox vaccine production. Rather, it has been used in testing of new vaccines.

[9] WHO (2009). WHO Advisory Committee on Variola Virus Research: Report of the Eleventh Meeting. WHO/HSE/GAR/2009.3, p. 1.

[10] US Centers for Disease Control (2003). Smallpox Fact Sheet: Vaccine Overview, p. 2. URL: http://www.bt.cdc.gov/agent/smallpox/vaccination/pdf/vaccine-overview.pdf

With multiple safe and effective vaccines already available and stockpiled, there is no compelling reason to continue to authorize temporary retention of variola for development of additional, non-essential vaccines that do not manifest a take.

Animal Model: Variola virus is not known to naturally cause illness in any other species, making smallpox a uniquely human disease. Developing a useful animal model of human smallpox has proven impossible to date, despite repeated dangerous experiments in the United States involving injecting large amounts of variola virus into large numbers of primates and other mammals.

For years, US Department of Defense-linked scientists attempted to create variola infections in monkeys that mimic human smallpox. In these experiments, the 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 disease by inoculating them with huge doses of variola. These monkeys, however, did not display disease corresponding to the early stages of human infection. Instead, they immediately progressed to advanced illness and died or were euthanized. Despite repeated experiments, primates simply have not been induced to develop disease with strong parallels to the course of human infection.

The failure of the primate model has been apparent for a number of years. Despite the absence of promising results, WHO has allowed experiments to continue. This appears to be related to the convergence of US policy goals (retaining variola virus stocks) with the personal will of a US health ministry official (and former military biodefense researcher), who himself is the author of papers on the animal model experiments.

More recently, US researchers have infected prairie dogs with variola virus. These experiments have also failed. Animals were inoculated intranasally or through scarification (application of virus to the skin by needle scrapes). Neither group became ill, and it was concluded "*the prairie dog was not considered a good animal model for variola virus infections*."[11]

Thus, there is no valid animal model of human smallpox disease that uses variola virus in sight and there are no promising prospects of developing one. Fortunately, however, with effective vaccines and diagnostics, there is no essential need for a model, because the R&D necessary to develop effective means to detect and combat any future smallpox outbreak has already been done. In addition, development of an animal model of human smallpox infection using orthopoxvirus(es) other than variola (e.g. monkeypox) remains a possibility that could be scientifically useful, without need for variola.

Moreover, model development itself is a particularly risky activity involving culturing large amounts of virus, injecting or aerosolizing it, creating dangerous infected animals, and potentially exposing relatively large numbers of humans to live virus. Continued animal model experiments with live variola solely serve the purpose of heightening the chances of a tragic accident or escape of this dangerous virus.

As the VAC itself is considering,[12] the time has come for animal experiments to end. The VAC has been over-tolerant of failed and dangerous animal model experiments in the US. **The VAC's belated decision to reconsider work on the primate model at its next meeting in November 2010 should not preempt WHA action to terminate animal model experiments sooner,** particularly in light of

---

[11] WHO (2009). WHO Advisory Committee on Variola Virus Research: Report of the Eleventh Meeting. WHO/HSE/GAR/2009.3, Executive Summary.

[12] In the report of its 11th Meeting (WHO/HSE/GAR/2009.3), the VAC notes: "*the Advisory Committee will evaluate at its next meeting whether further evaluation of the non-human primate model of variola virus infection is deemed appropriate*" (p. 2).

the VAC's history of domination by the interests of Northern scientists with personal or institutional interests in expansion of variola research.[13]

Antiviral Drugs: Like the other purposes for which WHA previously authorized continued temporary retention of variola virus, no essential reason remains to retain the virus for the purpose of development of antiviral drugs.

To discuss use of variola virus for development of antiviral drugs, it is important to bear in mind some basic facts:

> *First*, even if smallpox antivirals are licensed, from a public health standpoint, vaccination will remain the primary means of combating any future epidemic, a conclusion that the VAC, IOM committee, and veterans of the WHO Smallpox Eradication Program all share. Antivirals would primarily be used with those individuals unfortunate enough to have been infected prior to the deployment of WHO's vaccine stockpile.
>
> *Second*, post-exposure treatments for variola do exist. At least one vaccine, Dryvax, can be administered up to a week post-exposure and prevent or lessen the severity of smallpox disease. Experimental antivirals also exist, with orthopoxvirus-specific and other modes of action. These may be used to provide compassionate care for infected individuals. Some of these antivirals risk side effects (which make them difficult to license), however, as the VAC has noted, these risks may be acceptable in the context of smallpox disease. [14]
>
> *Third*, achieving licensure of an antiviral to treat a disease for which there are no human cases to demonstrate efficacy is a very difficult task. This is particularly the case because there is no good animal model for human smallpox infection, and little prospect for one being developed using variola virus as the disease agent. With the pathway to licensure unclear and, if it is possible at all, a license likely requiring the standard rules to be bent, the development of smallpox antivirals threatens to become an endless activity. The IOM committee in the United States, in its most dubious conclusion, has already suggested as much (see page 11).
>
> *Fourth*, antiviral drug development is typically a lengthy, proprietary, costly, and frequently unsuccessful endeavor. For instance, consider costs: A widely-cited 2003 paper put the average cost of new drug development at US $802 million per medication.[15] A more recent estimate pegged average costs at US $1 billion, depending on the company and the drug.[16] And the cost of anti-infection drugs is estimated to be higher than average.[17]

Consideration of retention of smallpox stocks for antiviral development thus requires review of progress to date and weighing this progress (and the possibilities of success) against the risks of not destroying the virus.

Some progress has been made in antiviral development. One compound, called ST-246 and owned by the US company Siga Pharmaceuticals, is effective against variola *in vitro* and has thus far proven safe in human trials. It has also been used, under special authorization, against a case of Eczema vaccinatum, a dispersed vaccinia infection that is a rare side effect of smallpox vaccination.[18]

---

[13] See: Third World Network and the Sunshine Project (2005). The Genetic Engineering of Smallpox. URL: http://*www.biosafety-info.net/file_dir/413148854af122567.pdf*

[14] WHO (2008). WHO Advisory Committee on Variola Virus Research: Report of the Tenth Meeting. WHO/HSE/EPR/2008.9, p. 2.

[15] DiMasi JA et al. (2003) Journal of Health Economics 22: 151–185.

[16] Adams CP, Brantner VV. (2010) Health Econ. 19: 130–141

[17] DiMasi JA et al. (2004) Drug Information Journal 38(3):211-23

[18] The patient was the child of a US soldier who was vaccinated against smallpox. The child is thought to have acquired vaccinia from the father shortly after his inoculation and to have then developed the rare severe

Another smallpox antiviral, called Cidofovir, demonstrated *in vitro* activity against variola but its development stalled due to toxicity and other issues. It has recently been chemically reformulated to decrease kidney toxicity and increase its bioavailability. The reformulated Cidofovir has also proven more effective against variola *in vitro*. Called CMX001, the formulation is proprietary to Chimerix, another US company. Unlike Siga and ST-247, Chimerix is primarily developing CMX001 for non-smallpox use to control viral infections in transplant patients, but has received a grant from the US government to pursue its use against variola.[19]

Both of these candidate antivirals are working toward licensure in the US, with ST-246 considerably more advanced in the process. Much lack of clarity remains, however, concerning approval, manufacture, and distribution. Because of the lack of human smallpox cases and validated large animal model, the path to licensure is uncertain. In addition, the market and cost of these proprietary antivirals, if licensed, is unclear. It seems unlikely, however, that most countries would choose or could afford to stockpile smallpox antivirals given other public health priorities.

Upon balancing concerns, it is clear that WHA can move to withdraw approval for retention of virus stocks for antiviral development. Both ST-246 and CMX-001 have demonstrated activity against variola and can continue the process of testing and regulatory approval without variola virus (including animal models that use alternative orthopoxviruses). Drug development from scratch, however, poses the threat of becoming interminable, is costly and unlikely to succeed, and also unlikely to result in a drug that is affordable and available in quantity to the vast majority of WHO Member States. And it should be recalled that even if available, antivirals would not constitute the primary line of defense against an epidemic (which is provided by vaccines).

Furthermore, even if ST-246 and CMX-001 ultimately fail to achieve licensure due to the lack of an animal model of smallpox acceptable to US regulators, these and other drugs that are likely to be effective against smallpox will be available for special emergency use in the event of an outbreak. Moreover, human safety trials can be conducted without variola virus. While such use of such drugs may pose somewhat greater risks than on-label use of licensed pharmaceuticals, smallpox infection is a far from normal occurrence for which strong arguments can be made that normal requirements be relaxed due to extraordinary circumstances. (As US regulators have already done in the unusual child case of Eczema vaccinatum.)

Preordained Conclusion: The US Institute of Medicine Committee

In 2008 the Institute of Medicine (IOM) of the US National Academies of Science formed a committee to assess future scientific uses for variola virus. Named the *Committee on the Assessment of Future Scientific Needs for Live Variola Virus,* it was the successor to another, similar IOM committee that released a report on variola virus in 1999, [20] shortly before the United States reneged on a pledge made by its health minister to destroy the virus stocks.[21]

After four meetings, in July 2009 the final report of this new committee, titled *Live Variola Virus: Considerations for Future Research*,[22] was published. This report was presented to the VAC at its 11th meeting in November 2009. At the WHA in 2010 and 2011, this report is likely to be presented

---

infection. CMX-001 was also used in this case. (See URL: http://www.nytimes.com/2007/05/18/health/18smallpox.html

[19] See URL: http://www.chimerix-inc.com/therapeutic-programs/category/cmx001/

[20] The 1999 report was titled *Assessment of Future Scientific Needs for Live Variola Virus.*

[21] In 1990, then US Secretary of Health and Human Services Louis Sullivan pledged: "*There is no scientific reason not to destroy the remaining stocks of wild virus. So I am pleased to announce today that after we complete our sequencing of the smallpox genome, the United States will destroy all remaining virus stocks.*"

[22] The report is available at URL: http://www.nap.edu/catalog.php?record_id=12616

as a scientific determination that variola virus stocks are essential for public health needs. This, however, would be a misrepresentation of the facts.

Skewed Charge: While chartered by the US Congress, the US National Academies are a non-profit organization. In studies of the type recently conducted on variola, the Academies act as a consultant to the US government. Because it commissioned and paid for the variola study, the US Department of Health and Human Services (HHS, the health ministry), through the US Centers for Disease Control, predetermined the scope of issues that the committee was permitted to consider.

The US government instructed the IOM committee ***not*** to consider destruction of variola virus and its benefits, or the risks associated with continued possession and manipulation of variola stocks.

Rather, the committee's charge was the opposite. HHS specifically instructed the committee to contemplate the future and to imagine possible, often hypothetical, uses for variola virus, without due consideration of WHO restrictions, particularly the WHA's requirement that research be limited to that which is essential for public health.

The US government's official in charge of the committee was retired US Army Colonel Gerald Parker. After leaving command of the US Army's biological weapons agent lab at Fort Detrick, Maryland, Parker first went to the US Department of Homeland Security, where he was put in charge of building new maximum containment labs to study biological warfare agents.

In that job, Parker stoked controversy. In 2004, the US political review *Congressional Quarterly* quoted Parker as saying he was willing to use genetic engineering to develop new human pathogens if the purpose was to defend the United States.[23] This activity was also endorsed by planning materials leaked to the press that described plans for new laboratories whose development Parker was supervising.[24]

Although Parker's military past and extreme views would seemingly make him an inappropriate choice for such responsibilities, he was then appointed to the US health ministry, where he commissioned the IOM's recent variola study. He was also appointed to the VAC by WHO (see page 13).

Parker personally gave the IOM committee its charge at the outset of its first meeting. He began by saying that the US government had already determined that there was an ongoing need for variola virus:[25]

> "*First, a few principles. HHS does believe that continued availability of live variola virus stocks are essential to the mission of supporting research, advanced development, procurement, and licensing of medical countermeasures against the threat of smallpox."*

Thus, before the IOM committee even started to study the issue, it was told that US policy had determined that there would be an ongoing need for the virus.

Parker went further to specifically prevent the committee from veering off a preordained course. Members were bluntly prohibited from considering virus destruction and specifically instructed to come to conclusions supporting the US policy of virus retention:[26]

---

[23] Congressional Quarterly Homeland Security, 23 September 2003. Reprinted in British American Security Information Council (BASIC) (2004), Biological Weapons Update, 30 September 2003.

[24] Korch G. (2004) Leading Edge of Biodefense: The National Biodefense Analysis and Countermeasures Center, 2004 US Department of Defense Pest Management Workshop, Jacksonville, Florida, 9-13 February 2004. Presentation slides at URL: http://www.cbwtransparency.org/archive/nbacc.pdf

[25] US National Academies, Institute of Medicine (2008). Committee on Assessment of Future Scientific Needs for Live Variola Virus (TRANSCRIPT), 2 October 2008, p. 75.

[26] Ibid, pp. 76-77.

"Now the debate and discussion on destruction versus retention: First, that is not the job of this committee…"

He continued:

"Our discussion… is not about debating the US government policy on virus retention or destruction. It should focus on the current and ongoing scientific needs for research and development that may require continued access to live virus."

Although Parker had just told the committee it should focus on science, he then veered into assertions about threats allegedly posed to the United States by foreign bioterrorists, alleging that "*the smallpox threat is real, it is coming from outside the United States".*[27]

Such claims by the US government, frequently made since 2001, have never been documented. They were proven false in the case of the Saddam Hussein government of Iraq, which US intelligence officials charged with possessing smallpox virus in late 2002, and Libya, which US officials said they suspected had an offensive bioweapons program, another bioweapons allegation that turned out to be untrue.

With that tightly restricted charge, and prejudicial fearmongering about bioterrorism, Parker told the IOM committee that its report would be "critical" information for the WHO's major review of smallpox research and the scheduled debate on virus destruction at the 64th WHA.

The committee's conclusions were thus preordained by its charge, and its purpose, from its outset, was to construct arguments for the US political effort to evade WHA decisions to destroy the virus stocks. The committee was precluded from looking at all evidence on virus destruction and government officials deliberately used unsubstantiated allegations about bioterrorism to try to shape the committee's conclusions.

It is therefore unsurprising that the committee concluded that there are ongoing scientific needs for variola virus. The committee was essentially not permitted to make any other conclusion.

What is remarkable, however, is how weak the committee's conclusions are despite the pressure heaped upon it to justify US policy. The committee's conclusions, which were carefully prefaced with important caveats,[28] are here related individually to the purposes for which WHA has authorized continued temporary retention of virus stocks:

Sequencing: Although the IOM committee wished to see more sequencing of variola, it conceded that variola virus stocks are not necessary for this purpose. The IOM finding that further sequencing is not

---

[27] "*We have information now regarding the interests of terrorists in obtaining biological agents and their attempts to develop weapons*," Parker ominously told the committee scientists, sounding more like an army colonel than a public health official, "*We would argue that the smallpox threat is real, it is coming from outside the United States…"* (ibid).

[28] The preface, emphasis added: "***This committee, like is predecessor in 1999, did not consider the risk assessment*** *or financial resources* ***required to undertake necessary or useful research, as these issues were beyond its scope.*** *In addition, since decision making can be based only on information at hand,* ***the committee recognizes that future technological advances or policy considerations based on assessment of the risk of an accident or intentional release of variola virus could alter the scientific landscape.*** *With these caveats, the committee offers the following conclusions, which are based on its evaluation of current scientific capabilities and are meant to address the question of whether live variola virus would be needed* ***should the recommended research be undertaken****."* (IOM 2009. Live Variola Virus: Considerations for Future Research, pp. 132-33). Recall that in addition to not considering safety issues, the committee developed its recommendations for research without applying essential public health purpose criteria from WHA decisions and without considering the alternative of virus destruction.

essential corresponds to the conclusions of the VAC[29] and further underscores the need for WHA to withdraw authorization for retention of variola virus for sequencing purposes.

Diagnostics (and, in the US view, Detection): "*The committee concludes that live variola virus is not required for further development and diagnostic methods*"[30] This straightforward conclusion, harmonious with those of the VAC, also again underscores the need for WHA to withdraw authorization for retention of variola virus for diagnostic development purposes.

Vaccines: "*The committee concludes that [the] current development and licensure pathway for first- and second-generation vaccinia vaccines that produce a 'take' does not require use of the live variola virus*." In other words, as is already well known, multiple effective vaccines exist that may be used in the future, if necessary, and these do not require variola virus.

The committee then concluded that the virus would be needed for new future vaccines that do not show a take (lesion at vaccination site). In this case, it should be recalled that multiple safe and effective vaccines already exist and are licensed, most recently Bavarian Nordic's new vaccine, and that the US committee was instructed to identify possible future uses of variola stocks without due regard to WHA decisions and balancing future use of the virus against the risks of research and the benefits of destruction.

Thus, the US conclusion that variola may be useful in development of future vaccines cannot be validly applied in the context of the WHA discussions because it was made without balancing important safety and public health considerations. Specifically, developing new vaccines *ad infinitum* is clearly not an essential public health activity when multiple effective vaccines already exist.

Antiviral Drugs: The IOM committee concluded that variola virus should be retained for development of antiviral drugs. In elaborating this conclusion, the committee also showed the limits of its charge and its lack of consideration of the WHA discussions. The committee saw drug development as a "long term effort" and, in essence, an unending process. The last ten years of variola virus research for antivirals, which have not yielded a licensed drug, are only the beginning in the committee's view. The committee said that even if multiple licensed antivirals existed, that "*there would still be gaps in information regarding their safety*", and that the virus would still be needed for further drug-related research.

In its discussion of antivirals more than anywhere, the effects on the committee of the charge it was given shine through. New and more drugs to treat any disease can always be said to be valuable; but are such drugs worth developing from a safety and public health standpoint? Especially when, as the committee itself notes, "*In the event of an outbreak, however, vaccination still would be the most effective means of preventing an epidemic."* [31]

Developing drugs to treat an eradicated disease cannot be used as justification to maintain the virus and hence the threat of the disease through escape from confinement, but such matters were beyond the scope of the committee's charge. In a world where virus stocks are destroyed, are multiple variola antivirals actually essential for public health? Or is the never-ending development of antivirals merely circular logic that can only be maintained so long as the US and Russia fail to destroy their virus stocks?

How would production and stockpiling of variola antivirals be managed without patient demand? Who would pay for it, and would doing this make sense when weighed against other demands for public health resources?

---

[29] See WHO/HSE/GAR/BDP/2009.3, p. 2.
[30] IOM (2009). Live Variola Virus: Considerations for Continuing Research, p. 135.
[31] ibid, p. 87.

Animal Model: After 10 years of animal model research using variola virus, the IOM committee opened its observations by stating, "*it should be emphasized that there is still no animal model that satisfactorily recapitulates all relevant aspects of human smallpox*." While the US may interpret this conclusion as an indication that more animal model experiments with variola virus are necessary, in truth, the consistent failure of animal model experiments indicates the need to terminate this risky and non-essential research. This is particularly true in view of the fact that one of the reasons that animal model research was authorized in the first place – vaccine development – has progressed to the point that it no longer needs the animal model (see page 5).

The IOM committee noted problems with current animal models that use variola and other orthopoxviruses but made no specific recommendations on animal models *per se*. It did, however, make remarks with respect to animal models using variola virus in other sections of the report. It said that an animal model would be needed for future development of new vaccines and in "discovery research" (see below), neither of which is essential for public health and, thus, these two conclusions are invalid in the WHA context.

The IOM committee also endorsed further development of an animal model using variola in order to develop future antivirals – a purpose that is also not essential (see page 7). Finally, the committee also noted the promise of alternatives such as monkeypox and, recalling the lack of progress, recommended that a review of research to date be made.

In sum, the IOM committee recognized failings to date and offered no compelling new reason to continue animal model research utilizing variola. Those reasons that it did offer to further develop an animal model – antiviral research, new generations of vaccines, and "discovery research" – are each not essential to public health, as discussed elsewhere in this paper. It should also be recalled that the committee was not asked to make a determination if an animal model utilizing variola was worth developing in light of risks associated with developing it.

Other Research: Finally, the IOM committee discussed use of variola virus in "discovery research" and endorsed research on variola functional genomics. For "discovery research" (e.g. for understanding human immunology functions not intrinsically related to variola), while encouraging such studies the committee conceded bluntly that such research is "not essential". Indeed, such academic inquiries clearly fall well outside variola virus uses permitted by WHA.

On functional genomics, the committee argued that such studies would assist development of new vaccines and drugs. Functional genomics, which is simply defined as studying virus interaction with its host cells, is a wide field with applicability to many types of non-essential research. It is a set of techniques, rather than a purpose in itself.

There is no need for WHA to contemplate, much less approve "functional genomics" studies *per se*. Opening a door to "functional genomics" as a justification for virus retention could unleash pressure for many new studies with no essential public health purpose.

In the interim before destruction of virus stocks, if a scientist wishes to perform a study using functional genomics techniques, he or she can attempt to justify this under one of WHA's existing permitted uses for variola (e.g. as essential vaccine or antiviral research) and then see if the proposed research meets VAC and WHA approval. Studies with variola must by approved under one of the limited essential public health purposes that WHA has permitted, and studies utilizing functional genomics techniques are no exception.

Advisory Committee Composition and Attendance

Established to control smallpox research in 1999 when the US and Russia and failed to destroy their virus stocks in accordance with WHA Resolution 52.10, by 2005 the VAC was suffering criticism from developing countries not only for its recommendation (later rescinded) to permit the genetic

engineering of smallpox; but for a number of structural problems. These include lack of transparency, under-representation of developing countries, appointing members and advisors with personal and institutional conflicts of interest, and abject failure to effectively oversee activities at the US and Russian labs with smallpox virus stocks.

Statistics: Statistical analysis of its 3rd through 6th meetings in (2003-2005), revealed massive bias towards the north – 82% of members, advisors and observers were from the North, and the committee did not have a single advisor from anywhere but the US, Russia, or Western Europe.

In Resolution 60.1 (2007), the WHA sought to address a number of the VAC's problems. In some areas, the VAC has made progress, while in others it remains stagnant.

In terms of appointments, the committee has added more Southern members, however, this step forward has been offset by the ranks of Northern advisors (often personally interested in smallpox research) and poor attendance from the South:[32]

11th Meeting (2009)	**MEMBERS**			**ADVISORS**			**OBSERVERS**		
	North	South	Total	North	South	Total	North	South	Total
Appointed:	12	11	23	34	4	38	-	-	-
Attended:	10	6	16	27	2	29	4	0	4

10th Meeting (2009)	**MEMBERS**			**ADVISORS**			**OBSERVERS**		
	North	South	Total	North	South	Total	North	South	Total
Appointed:	13	13	26	26	4	30	-	-	-
Attended:	10	6	16	23	2	25	3	0	3

As can be seen, although the committee itself it theoretically balanced, in practice and as has been the case since at least its 3rd meeting, Northern members are much more likely to attend meetings. And in the area of advisors and observers, the committee's meetings are physically dominated by the large number of advisors from the North, most of whom represent government agencies or companies with an interest in smallpox research.

Conflicts of Interest and Transparency: The committee has not been rid of individuals with conflicts of interest. Those presently serving include Dr. Ilya Drozdov, the director of VECTOR, the Russian lab holding variola virus stocks, Dr. Ali Shan Khan, a deputy director of the US Centers for Disease Control (which hold US variola stocks), and Dr. Gerald Parker, the same US official that commissioned the IOM study and whose political responsibilities include defending US retention of variola stocks.

It is particularly worrisome that the report of the 11th VAC meeting and most recent report to the Executive Board (EB126/18) both prominently draw Member States' attention to the IOM study, however, neither document notes the conflict between Dr. Parker's political role of commissioning

[32] Data from annexes to WHO/HSE/EPR/2008.9 and WHO/HSE/GAR/BDP/2009.3.

the report for the US government and WHO role to evaluate the report's scientific merits as a member of the VAC acting ostensibly as a technical advisor to WHO.

In the area of transparency, the VAC has made some insufficient progress. The VAC's "technical subcommittee" has long wielded extra power because it reviews and approves proposed variola virus research. While, at last, WHO has begun to more systematically review and track research, and now posts copies of summaries of approved projects on its website (with US activities significantly better documented than Russia's), the process by which approvals are made remains opaque. The subcommittee's membership remains secret, as do its forms, processes, and deliberations. It is thus impossible to determine if the subcommittee is balanced, free of conflicts of interest, and if and how it is applying the WHA criteria to the review of proposed research.

Problems Posed by Variola DNA Synthesis

Previous reports have focused on the complications to virus destruction posed by the growing ability of scientists to synthesize longer and longer DNA sequences up to and including viruses and bacteria.[33] While the experiment has not been performed and has been prohibited by WHA resolution, it is now technically possible for variola virus to be assembled from sequence data, at least at a small number of specialized labs. The number of labs capable of such activities is likely to increase in coming years.

This situation obviously changes the norm since the 1980s that smallpox and its genes were only potentially available from the two WHO Repositories. Indeed, this reality was disturbingly underscored when it came to light that in 2006, Sandia National Laboratories, a US weapons laboratory with no public health mission, was conducting experiments involving variola genes that it obtained not from a WHO Repository; but which it ordered from a gene synthesis company.[34] It does not appear that these experiments were ever reviewed by WHO.

WHO has responded to this problem by publishing, in May 2008, a short paper titled *WHO Recommendations concerning the distribution, handling and synthesis of Variola virus DNA*, which has been posted on the WHO website.[35] It can be hoped that synthetic biologists will pay attention and will not be confused by the term "recommendations" in the title of a document that mainly reflects rules that should be mandatory pursuant to WHA resolutions.

As yet, however, effective regulation of gene synthesis companies does not exist in most countries (including the US), and the threshold for variola DNA synthesis length (500 contiguous bases) before WHO approval is required can be accomplished with "consumer level" DNA synthesizers found in basic biotech research labs and offered for sale to the general public. This heightens the risk of unauthorized variola DNA synthesis, either through ignorance of WHO rules (a considerable concern) or deliberate violation of them (a less likely but possible scenario).

The emerging problems posed by synthetic biology, which are not limited to those relating to variola, underscore the urgency of destruction of virus stocks. Once WHO Repository stocks are destroyed, possession of variola virus or quantities of variola DNA greater than the short sequences needed for diagnostics can be more clearly defined as a criminal act, enabling a meaningful implementation of the oft-heard goal of making possession of variola virus a crime against humanity.

---

[33] See: Lim Li Ching (2007). WHO Board urged to act on worrying smallpox research trends. Third World Network. URL: http://www.twnside.org.sg/title2/health.info/twninfohealth068.htm

[34] These experiments were revealed in the minutes of meetings of Sandia's biosafety committee. Sandia refused public comment on the research. The minutes suggest that the experiments related to a military biological weapons detection system.

[35] See URL: http://www.who.int/entity/csr/disease/smallpox/SummaryrecommendationsMay08.pdf

So long as the repository virus stocks remain, and lengths of variola DNA are distributed and possessed for non-diagnostic purposes, ill-defined grey areas will exist, illegal possession will be facilitated by ambiguous rules, and full criminalization of variola possession will not be possible.

The best way for WHA to respond to the problem of synthetic variola DNA and the possibility of synthesis of the entire virus is to rapidly destroy existing stocks so that variola possession can be fully criminalized at the national and international levels, removing any ambiguity that any person who possesses virus or who synthesizes large portions of its genome has committed a crime against humanity.

In addition, WHA can and should further clarify its restrictions on synthesis of variola DNA in the interim before destruction of virus stocks by expressly prohibiting variola DNA synthesis outside of WHO Repositories, requiring proposed research with synthetic variola genes outside of the Repositories to provide an essential reason that meets WHO approval for why such research cannot take place at the Repositories, and clarifying that variola genes transferred outside the WHO Repositories for approved research must be destroyed immediately upon completion of the research or upon WHO request, whichever is sooner.

Conclusions and Recommendations

The two countries that retain variola virus do so not for any defensible or essential public health reason. They do so out of exaggerated and unsubstantiated security concerns and mutual suspicions between them. Yet the strains of variola they thus far refuse to destroy are not private virus collections. Rather, they are WHO Repositories of strains collected decades ago in many corners of the world, placed in the repositories at the request of WHO, and only temporarily retained at the discretion of the WHA.

Two countries, making dubious and sometimes cleverly disguised arguments about their own interests and rivalries, cannot be allowed to continue to pose a public health menace to every other country in the world. While all people are threatened by the accidental or even deliberate release of variola from Russian or US labs, it is developing countries that run the greatest risk of catastrophe from smallpox, historically the greatest scourge of the human race.

WHO has initiated the major review of variola virus research requested in WHA Resolution 60.1. Literature reviews in the relevant scientific areas have been completed and are to be reviewed by a committee of independent experts appointed by the Director-General.

This independent committee will consider the literature reviews and will identify gaps remaining, if any, and assess the "outcomes for public health". This report will return to the VAC, presumably at its November 2010 meeting, and from there to the January 2011 Executive Board and the 64th World Health Assembly.

The composition of the independent committee is unknown and is of some concern in light of WHO's failure to remove conflicted individuals from the VAC and past imbalances in that committee. Moreover, because the committee is tasked with assessing public health outcomes, its membership should predominantly reflect the broader international public health community and not the narrower interests of orthopoxvirus researchers.

Indeed, the review is guided by WHA resolution 60.1, which assigns it a purpose: "*so that the Sixty-fourth World Health Assembly may reach global consensus on the timing of the destruction of existing variola virus stocks*." Thus the review must not become an exercise that simply looks at the research that has been undertaken. Rather from a public health perspective it must weigh the benefits of continued research against the benefits of destruction and explicitly identify what further research is essential (and not essential) for global public health purposes, if any, so as to come to consensus on destruction of variola stocks.

The balancing of interests to be performed by WHO and the WHA is fundamentally different than the speculative study conducted by the IOM Committee, whose charge can be paraphrased (our words) as "*What might you want do with variola virus in the future if it was decided that we would keep it, and you paid no attention to safety and cost issues or criteria from WHA resolutions?*"

Fixing a date for destruction of virus stocks is the obvious priority for the 64th WHA, however, action on the major review in 2011 does not preclude steps in the interim to facilitate the 2011 debate.

Items that Member States may wish to underscore in 2010 include:

- **The urgency of fixing a specific and prompt destruction date for remaining virus stocks, even if voting is required, and the necessity of following through on that commitment.**

- **The need for WHA to explicitly withdraw its authorization for continued temporary retention of virus stocks for purposes for which the virus is no longer required. The first, and easiest, of these are sequencing and diagnostics, which the VAC has repeatedly concluded no longer require variola virus. These can be followed by vaccines, the animal model, and antivirals.**

- **So-called "discovery research" and exploitation of new genetic techniques ("functional genomics") *per se* is not and has never been authorized by WHA and is not essential to public health.**

- **The WHA has never authorized open-ended, *ad infinitum* variola virus research. Rather, the WHA has only authorized research in specific areas that is essential to public health, and only in the temporary period before destruction of virus stocks.**

  Further to this point: WHA has not authorized ongoing research in areas where essential public health needs have been met (e.g. sequencing and diagnostics, and vaccines), nor has it authorized continued use of variola virus in projects that fail to produce significant public health benefits (animal model), nor has WHA authorized research where cost-benefit and risk analysis from a public health perspective shows that further use of variola virus is not essential (antivirals).

- **Recent scientific developments in DNA synthesis heighten the urgency of destruction of variola virus stocks and highlight the need for WHA to strengthen its control with additional restrictions specific to synthetic variola DNA.**

- **Request the Director-General to increase her efforts to reform the VAC (per WHA 60.1), particularly to implement transparency of the VAC scientific subcommittee, eliminate conflicts of interest in VAC membership, and ensure more balanced attendance of its meetings by members and advisors.**

- **Request the Director-General to increase transparency of the major review of variola virus research underway by releasing the membership of the independent committee and reports of its meetings, so that it may be ensured that the independent committee is free of conflicts of interest, geographically balanced, and incorporates broad public health interests.**