Third World Network
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Update on the Status of WHO Authorized Research Involving Variola Virus

INTRODUCTION

At the 60th World Health Assembly (WHA), Member States commissioned a Major Review of WHO-authorized research involving variola virus stocks. This Major Review was tabled in 2011 for discussion at the 64th WHA, which deferred a decision on fixing a date for destruction of smallpox virus stocks until the 67th WHA, which will convene in May, 2014.

In 2011, we published a lengthier report interpreting the WHO's Major Review of WHO authorized research utilizing variola virus. The Major Review documents,[1] one authored by experts in public health[2] and the other by specialists in orthopoxviruses, and our analysis of them, *Smallpox Virus Stocks at the 64th WHA: Implementing the Conclusions of the Major Review*,[3] remain important sources for the ongoing discussion. These sources have been updated in reports released by WHO in late 2013.

This update does not recapitulate the history of the WHO authorized research program but rather supplements it with interpretation of WHO publications on scientific developments since the release of the Major Review in 2011. It is primarily based upon the report of the November, 2013 meeting of the Advisory Group of Independent Experts to review the smallpox research program (AGIES), and the reports of the 14th and 15th meetings of the WHO Advisory Committee on Variola Virus Research (ACVVR), the committee that directly oversees the research program.

DEVELOPMENTS

Continued retention of variola virus stocks and their use at the WHO Repositories in the United States and Russia is restricted to WHO-approved essential public health research in specifically authorized areas: sequencing, diagnostics, vaccine development (primarily an animal model of human infection), and development of antiviral drugs.

The most significant development since 2011 has occurred in the area of antiviral drugs, a topic of particular controversy in the past because of disagreement over the ongoing need for live variola virus for this specific purpose. Previously, the United States has claimed a need for the virus in order to conduct studies necessary to achieve licensure of smallpox antiviral drugs. Recently, however, the US Food and Drug Administration (FDA) advised drug

[1] For direct links to these documents, WHO/HSE/GAR/BDP/2010.4 and WHO/HSE/GAR/BDP/2010.3, as well as WHA resolutions and other WHO documents historically significant to smallpox virus discussions, please visit: http://smallpoxbiosafety.org/resources.html

[2] This group, whose mandate was renewed by the WHA in 2011, is the *Advisory Group of Independent Experts to review the smallpox research programme*, abbreviated AGIES.

[3] Available at URL: http://www.smallpoxbiosafety.org/papers/WHAvariola2011.pdf

developers that the regulatory route to licensure of current candidate compounds (as well as new vaccines) does not require studies or data necessitating further use of live variola virus.[4]

Although we have previously argued, and continue to maintain, that licensure of antivirals is not an essential research purpose to retain the virus from a public health perspective,[5] the FDA's clarification that the regulatory pathway does not require further use of the virus eliminates the key scientific basis of the US objection to destruction of the virus.

Also of note with respect to antivirals, the United States government has placed a US $433 million order for 1.7 million courses of one candidate antiviral, ST-246, despite the fact that it is yet to be approved. Under a contract option, the US government can expand its purchase to 12 million courses.[6] The decision to stockpile the drug indicates very high US confidence in the efficacy of the compound, despite a lack of formal licensure.

The following chart describes the status of the research program (as of late 2012), broken down by WHO authorized research goals:

[4] See the report of 14th meeting of the ACVVR, WHO/HSE/PED/CED/2013.1, pp. 13-14.

[5] This is because in the unlikely event of any future smallpox outbreak, the primary means of containment will be vaccination. While antivirals may be of individual health care value in treating those unfortunate enough to be infected prior to containment of the virus, from a broad public health perspective, eliminating new infections by case isolation and vaccination are the means of response, whereas treatment of individual infections of those already infected is not the overriding public health concern. Further, previous studies have indicated that existing smallpox vaccines may be administered shortly *after* exposure to variola virus and still have a protective effect.

[6] SIGA Technologies (2011). SIGA Technologies Awarded U.S. Government Contract Valued at Up to $2.8 Billion (press release). 13 May. URL: http://investor.siga.com/releasedetail.cfm?ReleaseID=577406

SUMMARY OF THE COMPLETION STATUS OF WHO-AUTHORIZED RESEARCH INVOLVING VARIOLA VIRUS

Goal	Status	Comment
Virus sequencing	Completed	Dozens of viruses were already sequenced years ago, but WHO continues to receive new requests from the US and Russia to sequence still more. The ACVVR has repeatedly concluded that sufficient viruses have been sequenced for public health purposes.[7] The AGIES have also concluded "*that there is no public health need for sequencing of additional variola virus isolates*."[8] In 2012, the ACVVR denied authorization for a new proposal to sequence additional virus isolates.[9]
Diagnostics	Completed	Sufficient accurate and rapid diagnostics exist, with no ongoing need for virus. WHO is deploying these tests in a Smallpox Laboratory Network. The AGIES "*believes that there is no need to use live variola virus for work related to development and improvement of diagnostic tests for this infection."*[10] Nevertheless, the US and Russia continue to propose use of variola virus for development of additional diagnostics. Diagnostics in general are an area of active product development, and there will always be the possibility of putting new twists on previous approaches, but the <u>essential public health need</u> for reliable diagnostic tests has been fulfilled.
Animal Model (for vaccine development)	No remaining essential public health purpose	For over a decade, an animal model of human smallpox has been actively sought. Experiments in primates and other mammals have repeatedly failed, as animals have not developed disease that follows the course of human infection. This pattern continued in 2011 in failed experiments in mice. Not only is there is no good animal model for use in vaccine development; there is no need for one, as effective vaccines exist (see below). The AGIES concluded: "*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*."[11] AGIES suggests, as have ACVVR members, use of models using other orthopoxviruses (e.g. monkeypox in monkeys) to supplant any use of variola virus.
Animal Model (for antiviral testing)	No remaining essential public health purpose	As noted above, no useful animal model exists, and repeated experiments have failed to develop one. Retaining virus for these experiments was justified by the alleged necessity of an improved animal model

[7] WHO/HSE/GAR/2009.3, p.2.
[8] WHO/HSE/GAR/BDP/2010.4, p. 27.
[9] WHO/HSE/PED/CED/2013.1, p. 5.
[10] WHO/HSE/GAR/BDP/2010.4, p. 31.
[11] WHO/HSE/GAR/BDP/2010.4, p. 29.

		using variola virus in order to achieve licensure of antiviral drugs.[12] In 2011, the AGIES concluded "*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 US regulatory requirements referred to are no longer applicable, removing this justification for retaining variola virus. In 2013, the AGIES concluded that no need for the virus remains for this purpose.
Vaccine development	No remaining need for variola virus.	Effective vaccines against variola virus infection have existed for many years and are what eradicated smallpox from the wild. Recent vaccine research has focused on new vaccines with fewer contraindications and side effects. These "second" and "third" generation vaccines, developed in several countries, have achieved regulatory approval, such as Imvanex (Europe) and ACAM2000 (US). These and other vaccines are well past the point of any need for validation in experiments utilizing live variola, and have even been stockpiled in a number of countries. The continued manufacture and use of smallpox vaccines (which use vaccinia virus) presents no ongoing need for variola virus. Like diagnostics, the broader evolution of biomedical research will continually present possibilities of creating still more vaccines, however, the essential public health need for variola virus for this purpose has been more than satisfied.
Antiviral drugs	No remaining need for variola virus.	Previous research in the US and Russia has demonstrated the efficacy of several antiviral candidates against variola. Two of these are in very advanced stages of development – one is even stockpiled. For several years, the US argued that retention of virus was necessary because it would be needed in procedures to achieve full regulatory approval of these drugs. As previously noted, however, this argument is no longer valid. The US and Russia continue to request WHO approval to initiate new research to identify new drugs (first steps in a process that can take decades), but as with other areas, the essential public health need has been satisfied, and new long term projects to develop duplicative treatments are clearly unwarranted.

[12] We have argued for years that this alleged "necessity" is false, however, it was not until recently that the position of US regulators coincided with ours.

OUTCOME OF THE LATE 2013 MEETINGS OF THE AGIES AND ACVVR

The AGIES: The Advisory Group of Independent Experts to review the smallpox research program (AGIES) first met in 2010, when it issued a report that substantially favored the destruction of variola virus stocks, finding little reason from a global public health perspective to retain them.[13]

Meeting for the second time in November 2013,[14] the AGIES members unequivocally concluded that no global public health reason remains to retain variola virus for sequencing, diagnostics, animal models, and vaccine development. On the sole remaining item – research on antiviral drugs – a majority of the AGIES concluded that retention of virus can no longer be justified from a global health perspective.

Put simply, it is the unanimous opinion of the AGIES that four of the five objectives of the WHA-authorized research program no longer require variola virus, and it is their majority opinion that the fifth doesn't either. Accordingly, it is the scientific judgment of the majority of the global public health experts appointed by the Director-General that there is no compelling public health purpose to continue to retain variola virus. As stated in the Secretariat report to the Executive Board: "Members of the Advisory Group concluded that there is no need, from a global public health perspective, to retain live variola virus for any further research."[15]

The ACVVR: Meeting in September 2013, the Advisory Committee on Variola Virus Research (ACVVR) also considered the accomplishments and future of the research program, reaching similar conclusions as the AGIES, with the exception of the question of research on antiviral drugs (including an animal model for that purpose). In the case of antivirals, a majority of ACVVR members felt the virus should be retained to attempt to develop a working animal model for antiviral testing.

WHO has frequently considered that completion of the antiviral program would be licensing of two antiviral compounds with different activity. Presently there are two antiviral compounds with different modes of action that are "*well advanced along the regulatory pathway to licensure*"[16] with demonstrated efficacy, and which are "*highly unlikely to fail*". And, even in the event of failure, most AGIES feel that "*suitable surrogate orthopoxvirus models exist.*"[17] Further, as previously noted, the US regulatory authority, the Food and Drug Administration, has stated that these drugs may be licensed without additional studies involving variola virus.

Nevertheless, some ACVVR members argue that efforts should continue to develop an animal model for testing antiviral drugs despite years of such efforts by experienced scientists having failed. Smallpox was eradicated without an antiviral drug, and because it is a uniquely human virus, and it has no natural animal reservoir, there are biological impediments to ever developing a satisfactory animal model.

An animal model utilizing variola virus may no longer be considered necessary for completion of the WHA-authorized research program, and continuing discussion of the model despite the licensibility of drugs meeting WHO criteria is a stalling game.

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[13] See our 2011 report at URL: http://www.smallpoxbiosafety.org/papers/WHAvariola2011.pdf
[14] WHO/HSE/PED/CED/2013.3
[15] EB134/34
[16] WHO/HSE/PED/CED/2013.2, p. 14.
[17] WHO/HSE/PED/CED/2013.3, p. 10.

The ACVVR: Composition, Regional Balance, Attendance, and Voting

Salient features of the ACVVR in comparison to the AGIES should be pointed out. Historically, a few Member States have exercised far greater influence over the ACVVR than others. In particular, the United States and Russia have insured themselves very strong, and generally imbalanced, representation, and the Committee's procedures for membership appointments and succession are far less clear than those of the AGIES.

In addition to the outsized influence of a small number of Member States in its membership, the ACVVR has been heavily weighted toward research specialists in orthopoxviruses. While there are understandable reasons for consulting these experts, the particular focus of many ACVVR members on orthopoxviruses and their professional links to the two WHO-authorized variola virus repositories has in the past obscured their public health judgment, as matters that are scientifically interesting for research specialists have been confused with essential public health purposes.

This problem was apparent in 2005 when the Director-General, with support from Member States, overrode the ACVVR's decision to permit genetic engineering experiments with variola, and the 58th WHA encouraged WHO to exercise stronger oversight (setting in motion the process that led to formation of the AGIES).

The ACVVR's historical imbalances reappeared in its 2013 meeting. The Committee is composed of 21 members, twelve from the North (including Russia), and nine from the South. Actually attending were fifteen members. These included ten from the North, and only five from the South. Attendees were thus heavily tilted toward the North (2/3), and the United States and EU in particular. Whereas the US and members of the European Union each had four members of the committee, there was no representation among the attendees from Latin America and the Caribbean, and only one Member each from SEARO, EMRO, and Southern WIPRO members.

There was even greater imbalance in Advisers to the Committee. Of this group of nineteen official appointees, fourteen were in attendance. Of the fourteen, thirteen were from the North. Of the thirteen from the North, six were from the United States and five from Europe (excluding Russia). With members and advisors taken together, 79% were form the North, and more than a third of the room (34%) was from the US alone.

It should thus be clear that the discussion and voting by ACVVR members in 2013 was heavily influenced by a small number of Member States, and that entire regions were barely represented while other regions and one country were overrepresented.

If the ACVVR membership and attendance were more geographically balanced, there is strong reason to suspect that the committee's vote on antivirals would have turned out differently.

THE POTENTIAL TRAP OF "USE TO COMPLETION"

The 2013 report of the ACVVR notes that, in the past two years, 135 variola virus samples were removed from storage and partially sequenced at the US repository. Of these 135 samples, seventy samples were "used to completion" in the sequencing process, meaning that they no longer exist. The ACVVR report, as well as the report of the Secretariat to the

Executive Board suggest that this process could represent a "*potential precedent for the progressive reduction of all live virus material held in the two* [WHO] *repositories*."

We believe this suggestion is a poor one for several reasons.

It should be recalled that the ACVVR concluded many years ago that sufficient sequencing of strains had been accomplished, a conclusion supported by the AGIES. Despite repeated conclusions by WHO committees that no more sequencing is necessary, US scientists proceeded to sequence portions of the now "exhausted" virus samples. The fact that the US could not be constrained from conducting research that WHO's experts have repeatedly concluded was not essential for public health indicates the danger of allowing the US-based repository to determine scheduling of destruction.

Secondly, the "progressive reduction" of stocks simply runs counter to the conclusions of the WHO's expert public health committee, the AGIES, who hold that there is no essential public health purpose to retain them. As retention serves no compelling public health purpose, permitting so-called "progressive reduction" would constitute the WHA ceding control of the WHO repositories to their host countries, itself a dangerous precedent. If there is no qualifying purpose to retain them, as has been concluded by WHO public health experts, then the stocks should be destroyed – not gradually reduced over many years in the course of potentially dangerous research that has been deemed non-essential.

Thirdly, the institution of a process of "progressive reduction" could give rise to endless debates over what should be destroyed when. These debates will likely center in the ACVVR, a committee with opaque procedures and overrepresentation from specific countries and scientists who have a vested interest in the continuance of research involving variola virus. It could have the effect of shifting the debate from one about fixing a date for destruction – WHA's goal for decades – to one over piecemeal steps, not essential for public health, yet that could stretch retention decades into the future.

If the WHA-authorized research program's need for variola virus stocks is complete, as the preponderance of public health and scientific opinion has concluded, then the stocks should be destroyed, and the WHA needs to fix a date for doing so. So-called "progressive reduction" is a distraction from the realization of this goal.

CONCLUSION

The disappearance of the US regulatory requirement that allegedly necessitated retention of variola virus for antiviral drug approvals for advanced compounds is a major advance toward destruction of smallpox virus stocks. It is no longer possible for the US to credibly argue that vaccine and, especially, antiviral drug development, require continued retention of the virus.

WHO's public health experts, the AGIES, have concluded that there is no essential public health reason to continue to the retain the variola virus stocks. Even the ACVVR, the committee that oversees the research program, has concluded that most elements of the WHA-authorized program have been satisfied. Were that committee not disproportionately tilted towards the interests of one Member State – US members cast 3 votes for virus retention in a committee with only 15 attending voters – the ACVVR, like the AGIES, would also have concluded that there is no valid reason to continue to retain the virus stocks.

The case for fixing a date for destruction of smallpox virus stocks is stronger than ever. With scientific rationale for retention reduced to non-essential purposes, and regulatory requirements for retention evaporated, it is little more than political will that remains in the way of fixing a new destruction date.