



Editorial

Why not destroy the remaining smallpox virus stocks?

After the declaration of world-wide smallpox eradication in 1980, the World Health Assembly (WHO) has repeatedly called for destruction of all known remaining stocks of the smallpox virus [1]. Officially, only the US and Russia have smallpox stocks, and neither, referencing the value of their research agendas, have destroyed their stocks. In response, WHO established an Advisory Committee on Variola Virus Research, created in 1998, to review the validity of research proposed using live variola virus, and to monitor research progress. This international committee has concluded that live variola virus is no longer necessary except to continue attempts to create an animal model that might closely mimic human smallpox, and thus assist in licensure of new generation vaccines and antivirals [2–6]. Importantly, both the Institute of Medicine and an independent committee organized to review the WHO oversight committee's work have reached similar conclusions [7,8].

A variety of scientific and political/ethical issues drive the arguments for keeping or destroying the official repositories of smallpox virus. The scientific reports referenced above have not addressed these political and ethical issues, and their scientific recommendations bear greater scrutiny. Below we briefly comment on these issues.

1. Scientific issues

Genomic issues: The smallpox virus is no longer needed to elucidate its genome. There have been 49 strains sequenced, with the sequences published and available to researchers. No additional strains need to be sequenced [2].

Diagnostic issues: There have been tremendous advances in orthopoxvirus diagnostics in recent years [3]. Different orthopoxviruses can be distinguished with real time PCR, and the genetic reagents for these tests are available for selected laboratories. Additional refinement can be made using other orthopoxviruses, or with sections of the genome of smallpox strains already sequenced.

Vaccine development issues: Effective vaccines have been produced that are less reactogenic than first and second generation vaccinia vaccines, and are very effective against other orthopoxviruses [4]. Similar statements can be made about two new antiviral agents [5]. The water-soluble and bioavailable analogue of cidofovir, CMX001, is highly effective against orthopoxviruses in vitro and in vivo. ST-246, which has a different mechanism of action and seems unusually non-toxic in humans, may be even more effective.

Animal model development issues: Animal models of human smallpox have proved difficult to perfect [6]. Variola is very

host-specific, which was a critical factor in the ability to successfully eradicate the virus. Infection of other mammals is difficult. High dose direct intravenous infection of cynomolgus macaques is promising, but does not perfectly replicate human smallpox. While there are a number of good animal models for other orthopoxviruses, the FDA requires data from two animal models that closely mimic human smallpox in order to license new vaccines or antivirals. While such models would be useful, there are no guarantees that there will ever be animal models that mimic the pathophysiology of variola virus in humans.

Viral reconstruction issues: It is now possible to reconstruct smallpox virus from the published gene sequences given access to modern viral genetics laboratory equipment [2,9]. It would be even easier to insert the relevant genes responsible for its pathogenicity into readily available strains of vaccinia or monkeypox. This development is a two-way street for those concerned with the destruction of the live virus stocks. If smallpox viral stocks are destroyed, they can be rebuilt if necessary, which makes destruction of the current stocks moot. This scientific development makes the political and ethical issues regarding destruction of virus stocks even more important.

Laypersons have claimed that live virus stocks are necessary to fight bioterrorist attacks using smallpox [10,11], but such an argument proceeds from false assumptions. Stocks of vaccinia vaccines exist in the US and many other nations, and in addition the WHO has built a vaccine stockpile in case of emergencies. The actions sufficient to contain possible bioterrorist attacks are isolation of patients, and identification and vaccination of all real and potential contacts.

Thus, despite the fact that prestigious groups have identified research that requires use of live smallpox virus, what little is necessary can be done or approximated using vaccinia, monkeypox, or partial fragments of the smallpox genome. These scientific possibilities, coupled with the ability to recreate partial or entire genetic sequences of the virus, suggest that retention of the live viral stocks is unnecessary, and represents an unnecessary risk to mankind.

2. Political/ethical issues

The United States has been a strong supporter of the World Health Organization and the United Nations. Failure to comply with the consistent request of the World Health Assembly jeopardizes our potential to work with the United Nations to further our own foreign policy and population health goals.

Some have suggested maintaining virus stocks in the event of biologic warfare foisted upon unsuspecting nations. The United States has strongly rejected the use of biological warfare weapons,

and in fact the development or use of offensive biologic weapons in the US was outlawed decades ago by President Nixon. Accordingly, we have banned such weapons as part of our military arsenal, and there is no plausible scenario whereby the US would use biologic weapons such as smallpox in an offensive or defensive posture. While the US is not using live smallpox virus for biological warfare research, keeping the stocks might easily be interpreted by rogue nations and/or terrorist groups as justification for their own biological warfare efforts.

This risk of a biological warfare attack using smallpox is intangible and likely infinitesimal. The former Deputy Director of the Soviet Union's BioPreparat has written that during the height of the Cold War there existed manufacturing facilities within the Soviet Union capable of producing smallpox virus in quantities of tons [12]. He claims that the State Research Center of Virology and Biotechnology (the VECTOR Institute), in Novosibirsk, Russia, pursued the possible use of recombinant products of smallpox virus as biologic weapons. These allegations have never been corroborated. In addition, we are unaware of any public statements by nation states or terrorist groups regarding development of smallpox as a bioweapon. The United States and Allied forces did not find evidence that smallpox virus existed in Iraq. No other published evidence suggests that smallpox is being illegally grown anywhere.

Nonetheless, suppose that a terrorist group had the sophistication to grow, lyophilize, and prepare smallpox virus for dispersal. Such sophistication would contain the realization that a successful attack could quickly result in irreparable harm to their home country. Once transmission is established in the target country, travelers can and would rapidly disperse it throughout the world. Most Western nations have the facilities to isolate patients and vaccinate contacts in a timely manner, but most less developed countries do not. Such nations would suffer disproportionately from "blow-back," a risk which proves a major deterrent for this means of terrorism.

Ethically we find it hard to justify maintaining an eradicated virus. An accidental release, no matter how small the risk, is an unacceptable risk; given the lack of any possible utility in keeping the virus. Maintenance of such stocks is expensive and places a burden on the Centers for Disease Control and Prevention that is unnecessary and scientifically without merit, and for which resources could be better used in protecting mankind from infectious diseases.

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. One of us (JML) has seen first hand the heartbreaking devastation of human smallpox.

The simple fact is that smallpox can now be reconstituted from published sequences if needed from a scientific point of view. Why keep the existing stocks? We risk the opprobrium of the rest of the world by keeping virus strains that have little utility, result in unnecessary risk and expense, and which may be seen by others as symbolic of a bioweapon arsenal. It is time to destroy our remaining smallpox virus stocks, call upon the rest of the world to do the same, and make possession of the virus an international crime against humanity. We find no evidence to compel us to do otherwise.

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