The Smallpox Destruction Debate: Could a Grand Bargain Settle the Issue?

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One of the longest and most contentious international policy debates has swirled around the question of whether to destroy the last known stocks of the smallpox (variola) virus, which are preserved at two World Health Organization (WHO)-authorized repositories in Russia and the United States. Although smallpox was eradicated from nature more than three decades ago, concerns surfaced in the early 1990s that a few countries may have retained undeclared samples of the virus for biological warfare purposes. Because a smallpox outbreak would be a global public health emergency of major proportions, in 1999 the WHO approved a research program at the two authorized repositories to develop improved medical defenses against the disease.[1]

In May the smallpox research program will mark its 10th anniversary, a milestone that has intensified the debate among the WHO's 193 member states regarding the disposition of the authorized stocks of the smallpox virus. Some analysts worry that the controversy may be headed toward a diplomatic confrontation that would be harmful to all concerned. This article reviews the current status of the smallpox debate, assesses its implications for biological arms control, and proposes a grand bargain to bridge the gap between the pro-destruction and anti-destruction camps.

History of the Debate

A contagious viral disease that infected only humans and had a mortality rate of about 30 percent, smallpox claimed hundreds of millions of lives over the course of history and left the survivors with disfiguring facial scars.[2] In 1966 the WHO launched a global vaccination campaign that over the next 11 years eradicated smallpox from the planet in one of the greatest public health achievements of the 20th century. Key to the success of this effort was the availability of a highly effective freeze-dried vaccine that was heat stable and, when suspended in saline solution, could be delivered into a recipient's skin by unskilled health workers. Another contributing factor was that the smallpox vaccine was not a killed or weakened form of the smallpox virus itself but a related live virus (initially cowpox virus, later vaccinia virus) that caused a mild infection but was similar enough to the smallpox virus to induce protective immunity against the far more deadly disease. After smallpox eradication was confirmed in 1980, most countries halted the routine vaccination of their civilian population.

Even before the last natural outbreak of smallpox was snuffed out in Somalia in 1977, the WHO sought to reduce the number of facilities holding stocks of the smallpox virus in order to prevent an accidental release that could lead to a reintroduction of the disease. In response to a 1975 survey of biomedical laboratories around the world, 74 reported possessing samples of the virus.[3] Concern about the risks of ongoing research with the live smallpox virus increased sharply after a laboratory accident in 1978 at the University of Birmingham in the United Kingdom caused two infections and one death. In response, the World Health Assembly, the WHO's top decision-making body of member

states, adopted Resolution 33.4 in 1980 urging all countries that possessed the smallpox virus either to destroy their stocks or transfer them to one of four designated WHO collaborating centers. Because the WHO did not have the authority or the ability to verify these actions by member states, the consolidation of the smallpox virus stocks took place on a good-faith basis.

In 1983 two facilities, the U.S. Center for Disease Control (CDC) in Atlanta and the State Research Institute for Viral Preparations in Moscow, became the sole authorized repositories of the smallpox virus.[4] These two sites were chosen because they had served as the WHO reference laboratories during the eradication campaign and thus possessed the world's largest collections of smallpox virus strains. But the poor physical security at the Moscow institute, combined with the political unrest that followed the breakup of the Soviet Union, prompted fears that the smallpox virus stocks stored there might be at risk. In 1994, without obtaining prior approval from the WHO, the Russian government moved the repository from Moscow to the State Research Center of Virology and Biotechnology "Vector" in the remote Siberian town of Koltsovo, near Novosibirsk. Today the CDC has 451 samples of 229 different strains of the smallpox virus, collected from outbreaks in various parts of the world during the eradication campaign, while Vector has 691 samples of 120 strains.[5] At each repository, the virus stocks are stored in liquid-nitrogen freezers and protected with elaborate security measures.

In 1990 a WHO scientific advisory committee recommended that all known stocks of the smallpox virus be destroyed by December 31, 1993, after the DNA sequences of representative strains had been determined for scientific and forensic purposes. Protests from the scientific community and delays in the DNA sequencing effort led the WHO to postpone the date of destruction. Meanwhile, in 1992 a high-level official in the Soviet biological warfare program named Kanatjan Alibekov (aka Ken Alibek) defected to the United States with some stunning information. He told the CIA that during the Cold War, the Soviet Union had developed a highly lethal strain of the smallpox virus as a strategic weapon and had produced and stockpiled several tons of the virus in the form of a liquid suspension.[6] Particularly troubling was Alibek's claim that the Vector laboratory had been directly involved in the weaponization of smallpox. Moreover. the secret development and production program had been in systematic noncompliance with the 1972 Biological Weapons Convention (BWC), to which Moscow was a party.

Alibek's revelations suggested that Russia and other states might have retained hidden caches of the smallpox virus in violation of WHO policy. The CIA subsequently obtained circumstantial evidence that undeclared stocks of the virus might exist in several countries of proliferation concern, possibly including but not necessarily limited to Iran, Iraq, and North Korea.[7] A few scientific research centers also reported finding and destroying vials containing the smallpox virus that had been retained inadvertently in laboratory freezers, sparking fears that other poorly secured samples might exist that could fall into the hands of terrorists.

These preoccupations, combined with the progressive decline in the proportion of the global population with persistent immunity to smallpox, the limited supplies of the smallpox vaccine, the lack of physician familiarity with the disease, and the increased density and mobility of urban dwellers in megacities throughout the developing world, stoked fears that a deliberate release of smallpox virus by a rogue state or terrorist group could result in a rapidly spreading epidemic, posing a grave threat to international health and security.[8] Most Americans born after 1972, except those who had served in the armed forces or traveled to countries where the disease was endemic, had not been immunized against smallpox and hence would be unprotected during an outbreak, while those vaccinated once in childhood were believed to retain only partial immunity.[9] The vulnerability to smallpox of much of the world's population could not be remedied by a return to universal vaccination because the standard vaccine was not risk free. Although the adverse effects, including the rare death, associated with the vaccination of otherwise healthy people could be tolerated when natural smallpox was widespread, these risks became unacceptable once the disease was eradicated. Moreover, no antiviral drugs had been licensed for the treatment of smallpox.

In 1996 the World Health Assembly adopted Resolution 49.10 recommending that the smallpox virus stocks at the CDC and Vector be destroyed on June 30, 1999. Over the next few years, however, the United States became increasingly concerned about the possible existence of undeclared stocks of the virus and the lack of effective medical defenses. In 1998 the U.S. government asked the Institute

of Medicine, a policy analysis arm of the National Academy of Sciences, to assess the scientific need for additional research with the smallpox virus. An Institute of Medicine expert committee released a report in March 1999 endorsing further work with the live virus to develop improved diagnostic tools, a safer vaccine, and at least two antiviral drugs that worked by different mechanisms.[10] The rationale was that in the event of a bioterrorist attack with the smallpox virus, the contagion might spread widely before large-scale vaccination could begin. Thus, therapeutic drugs would be needed to treat the first generation of cases and to help contain the epidemic.[11]

Responding to U.S. pressure, the World Health Assembly in May 1999 adopted Resolution 52.10 establishing a three-year program of applied research with the smallpox virus at the two authorized repositories. All access to the live virus would be confined to hermetically sealed biosafety level 4 laboratories at the CDC and Vector, where scientists work in full-body "space suits" equipped with individual air supplies to protect them from infection. The World Health Assembly also established a scientific oversight committee, the WHO Advisory Committee on Variola Virus Research, to review proposed experiments with the live smallpox virus and monitor their execution.[12] All approved research projects had to offer direct public-health benefits and could not be justified merely on the grounds of "interesting" science. The experiments also had to be "outcome-oriented and time-limited" and the results published in the scientific literature or summarized in abstracts posted on the WHO Web site. Finally, WHO member states would be guaranteed equitable access to the outcomes of the research, including antiviral drugs, vaccines, and diagnostic tools.

Although the United States wanted the smallpox research program to be open ended, India insisted on amending the resolution to state that all work with the live virus would cease at the end of 2002 unless the World Health Assembly made a positive decision to extend it. The draft resolution, as amended, was adopted by acclamation. In May 2002, following the fall 2001 terrorist attacks and anthrax mailings in the United States, the World Health Assembly adopted Resolution 55.15, which extended the smallpox research program at the CDC and Vector for an indefinite period and put off a decision on the timing of virus destruction until all of the research goals had been achieved.

Retentionists and Destructionists

Proponents of preserving the two WHO-authorized collections of the smallpox virus, known as retentionists, argue that the danger of a reintroduction of smallpox derives less from the known repositories than from unknown stocks of the virus that may be held covertly and illicitly for hostile purposes.[13] If this suspicion is true, then the destruction of the WHO-authorized stocks would be largely meaningless and could create a false sense of security. Retentionists also contend that ongoing research with the live smallpox virus is needed to develop medical countermeasures against its potential use as a military or terrorist weapon. Such defenses would have a deterrent value by reducing the impact of a deliberate release of the virus, thereby thwarting the attacker's objectives.

Over the past decade, the smallpox research program at the CDC and Vector has yielded a valuable collection of vaccines, antiviral drugs, and diagnostic tools, but further work with the live virus may be needed to secure regulatory approval for the use of new therapeutic drugs in humans and to gain additional insights into the disease process. For this reason, retentionists believe that it makes no sense to set an arbitrary deadline for destroying the WHO-authorized stocks until all of the research goals have been accomplished. Some retentionists also contend that samples of the smallpox virus may be needed in the future for scientific reasons that cannot be anticipated at present. According to a supporter of continued research with the live virus, "[T]here is no arguing that we live in a world where ignorance is more dangerous than knowledge.... The task of the medical research community is to anticipate future catastrophic scenarios by continuing to learn from our past adversaries."[14]

Retentionists reject the claim of some critics that U.S. possession of the smallpox virus serves a military deterrent function analogous to that of a second-strike nuclear capability. They note that the Nixon administration unilaterally renounced the U.S. offensive biological weapons program in November 1969 and that the United States became a party in 1975 to the BWC, which bans the development, production, and possession of biological weapons but permits research on pathogens for prophylactic, protective, and other peaceful purposes. The use of biological weapons in warfare is also explicitly banned by the 1925 Geneva Protocol, which the United States ratified in 1975. Thus, even if the United States was attacked with smallpox, it would not retaliate in kind but with other

forms of military power.

Proponents of destroying the authorized stocks of the smallpox virus, known as destructionists, argue that continued research with the live virus at the two WHO-approved repositories entails a small but finite risk of an accidental release. Moreover, although the smallpox laboratories at the CDC and Vector are well secured against intruders, any scientist with authorized access to the virus would be capable of smuggling out a small sample and transferring it to a rogue state or terrorist organization, which could then cultivate it in large quantities. This "insider threat" has been underscored by the FBI's assertion in August 2008 that the sole perpetrator of the 2001 anthrax letter attacks was Dr. Bruce E. Ivins, a respected microbiologist who had worked for decades at the U.S. Army's biodefense laboratory at Fort Detrick in Maryland.

Destructionists also argue that, from an international legal standpoint, the smallpox virus collections at the two WHO-approved repositories are not the property of the two host countries but are being held in trust by them for the benefit of the international community. If Russia and the United States continue to insist that access to the live virus is vital for their national security, then other countries may demand to participate in the research. According to a WHO survey in 2007 of states that had voluntarily transferred their smallpox virus collections to the Russian and U.S. repositories during the 1970s and 1980s, one of the seven respondents asserted that it retained "ownership rights" to the transferred stocks, while the other six said that they had waived such rights or had not addressed them in the accompanying documentation. (The identity of the state claiming ownership rights was not disclosed.) The WHO Secretariat concluded that "there appear to be uncertain, as well as variable, ownership scenarios for the stocks in question at the two repositories."[15]

As a practical matter, WHO member states agree that samples of live smallpox virus should never be removed from secure storage at the CDC and Vector. Nevertheless, if a country that transferred its stocks to one of the repositories were to seek access for some of its scientists to work with the live virus, the repository and the WHO would have to consider this request. The dilemma is that the greater the number of scientists granted access to the smallpox virus stocks, the higher the risk of an accidental release or a security breach.

Verification of Virus Destruction

Another thorny issue is how to verify the destruction of the known stocks of the smallpox virus held in Russia and the United States. Although the smallpox laboratory at Vector recently resumed research with the live virus after a hiatus of a few years for safety and security upgrades, its activities are far from transparent. Moreover, in contrast to the verification regimes for nuclear and chemical arms control treaties, no multilateral or bilateral mechanism is capable of verifying the complete and irreversible destruction of a self-replicating entity like a virus with a reasonable degree of confidence.

Even if the known stocks of smallpox virus in the two WHO-authorized collections were incinerated tomorrow, there would be no way of proving that samples of the virus had not previously been removed and stored elsewhere. Indeed, whenever scientists work with the live virus, they cause it to replicate, creating more of the deadly agent. The smallpox virus is highly stable when freeze dried or frozen in liquid nitrogen, making it easy to conceal seed cultures in small vials. Because the virus will replicate in fertilized eggs or cell culture, a tiny sample could be grown into a large quantity.

Further complicating the problem of verification is the suspicion that Russia and possibly other countries may possess undeclared stocks of the smallpox virus outside the two WHO-authorized repositories. Given these concerns, a comprehensive verification mechanism would have to include a provision for short-notice challenge inspections of suspect facilities anywhere in the world. To provide an adequate level of confidence, such inspections would be highly intrusive and without right of refusal, yet it is unlikely that Russia, the United States, or any other country suspected of having clandestine stocks would agree to such an "anywhere, anytime" inspection regime.

Impact of Emerging Biotechnologies

Advances in biotechnology are also changing the nature of the smallpox debate. Until now

discussions in the World Health Assembly have proceeded on the assumption that the destruction of the virus stocks would be final and irrevocable, but that may not be the case much longer. The development in the early 1980s of automated DNA synthesizers capable of making customized strands of genetic material from off-the-shelf chemicals, and the steady improvement of this technology over the past 25 years, have now made it possible to produce long fragments of synthetic DNA in the laboratory and assemble them into genes and even entire microbial genomes (the genetic blueprints of living organisms). As DNA synthesis technology continues to progress at a rapid pace, it will soon become possible for cutting-edge scientists to re-create any virus whose genetic sequence has been determined, including the smallpox virus.

Already, U.S. researchers have overcome the technical challenges associated with synthesizing a DNA molecule as large as that of the smallpox virus genome, which consists of about 186,000 DNA units, or base pairs. In January 2008, the J. Craig Venter Institute announced the synthesis of a stripped-down bacterial genome made up of 582,970 base pairs, or more than three times the size of the smallpox virus genome.[16] A second hurdle to re-creating the smallpox virus in the laboratory is the fact that the "naked" viral DNA is not infectious by itself and requires enzymes present in the virus coat to replicate in the host cells, but techniques are already available for working around this problem. At its 2008 meeting, the WHO Advisory Committee on Variola Virus Research discussed the potential laboratory synthesis of the smallpox virus and concluded that the remaining technical obstacles could be overcome.[17]

Although the WHO prohibits any lab outside the two authorized repositories from possessing smallpox DNA that exceeds 20 percent of the viral genome, the organization has no way of enforcing this rule. Thus, when it becomes possible in the near future for a technically proficient laboratory to synthesize the smallpox virus, the risk of hostile use will expand beyond any illicitly retained stocks of the virus to include an artificially created weapon. Retentionists contend that the impending ability to create the smallpox virus de novo will render the destruction debate effectively moot. They also warn that within a decade, the technologies and know-how required for viral synthesis may have proliferated widely, making the need for effective medical countermeasures against smallpox more urgent than ever. Destructionists counter that the risk of de novo synthesis makes it all the more essential to prohibit the possession of the smallpox virus in any form, whether natural or artificial. In their view, destroying the WHO-authorized stocks would make it possible to brand any future retention, synthesis, or hostile use of the virus as a crime against humanity, punishable with the most severe economic, political, and military sanctions. Allowing the two existing repositories to retain their stocks of the virus indefinitely would seriously weaken the normative power of such a ban.

Another way that advances in biotechnology have complicated the smallpox destruction debate is by expanding the risk of potential misuse beyond the smallpox virus itself. Some biosecurity experts worry that a state or terrorist group seeking biological weapons would be more likely to use classical genetic engineering techniques to create more deadly forms of other poxviruses that infect humans, such as monkeypox, cowpox, camelpox, and vaccinia (the smallpox vaccine). In their natural state, these viruses cause relatively mild disease and do not spread readily from person to person, but it might be possible to engineer them to become as lethal as smallpox if not more so. Such modifications might involve the insertion into the virus of a toxin gene or, alternatively, a gene coding for a substance that enables the virus to evade or suppress the human immune system.

In 2001, for example, Australian researchers reported that splicing the gene for interleukin-4, a protein that modulates the immune system, into the mousepox virus dramatically increased the virulence of the virus so that it could kill mice that were genetically resistant to mousepox or had been vaccinated against it. A similar genetic modification to a poxvirus that infects humans, such as cowpox, monkeypox, or vaccinia, might enable the engineered strain to cause a fatal disease even in immunized people. Monkeypox virus is endemic in rodents living in parts of central and western Africa and hence would be relatively easy for would-be bioterrorists to acquire. Moreover, because monkeypox naturally infects humans and nonhuman primates, a rogue scientist seeking to turn the virus into a biological weapon could test the lethality of genetically engineered strains in monkeys. Alibekov's revelation that the Soviet biological warfare program experimented with the genetic engineering of vaccinia and other poxviruses has also raised concerns that former bioweapons scientists with this expertise, some of whom are living abroad, might transfer the relevant know-how

to states pursuing biological arms or to terrorist organizations.[18]

In sum, retentionists are correct that destroying the WHO-authorized collections of smallpox virus in Russia and the United States would not eliminate the potential risks associated with (1) any illicit stocks that may exist in countries of proliferation concern, (2) the de novo synthesis of the smallpox virus, or (3) the genetic engineering of an animal poxvirus to render it highly virulent in humans. At the same time, destructionists have a valid point that continued research with the smallpox virus at the CDC and Vector would entail safety and security risks and is likely to provoke growing political controversy.

Averting a Diplomatic Disaster

Now that the WHO-approved smallpox research program has reached the 10-year mark and many of its primary objectives have been accomplished, the international debate over virus destruction has re-emerged with a new intensity. Because the developing countries of Africa and Asia suffered disproportionately from the ravages of smallpox during the decades prior to eradication, they have a strong emotional stake in the issue and view the continued existence of the virus as a potential threat. At the 2006 World Health Assembly, 46 states from WHO's Africa region, supported by Jordan, Iran, and Thailand, tabled a draft resolution setting a new deadline of June 30, 2010, for destroying the smallpox virus stocks at the CDC and Vector. The United States, Russia, and a few other countries blocked adoption of the resolution.

The following year, the 2007 World Health Assembly approved Resolution 60.1 affirming "the need to reach consensus on a proposed new date for the destruction of [smallpox] virus stocks, when research outcomes crucial to an improved public-health response to an outbreak so permit." To help build an international consensus, the member states requested the WHO director-general to conduct "a major review in 2010 of the results of the research [with the smallpox virus] undertaken, currently under way, and the plans and requirements for further essential research for global public health purposes."[19] Based on this review, the Sixty-fourth World Health Assembly in May 2011 will attempt to reach global agreement on the timing of destruction. (Coincidentally, the seventh review conference of the BWC has been scheduled for the fall of 2011, but the United States has not used BWC-related meetings to raise concerns about the possible existence of illicit smallpox virus stocks because the supporting evidence would probably be classified, less than conclusive, and almost impossible to prove even if correct.)

In order to prepare for the 2010 major review of the smallpox research program, the U.S. government has asked the Institute of Medicine to update its influential 1999 report on scientific requirements for the live smallpox virus. At the kickoff of the institute's study in October 2008, the government's charge to the expert committee was to "perform a comprehensive evaluation of the research and development work recommended in [the first] report and completed to date, and consider what unmet needs still exist that require the use of live [smallpox] virus."[20] The report, to be completed this year, will likely have a significant impact on the subsequent WHO review.

Meanwhile, an international political imbroglio is brewing over the smallpox destruction issue. Because any WHO member state can call for a voice vote or a roll-call vote at the World Health Assembly, a possible scenario for 2011 is that the African countries will propose a resolution setting a firm date for the destruction of the smallpox virus stocks at the CDC and Vector, and a large majority of member states will vote to endorse it. In that case, Russia and the United States would face a difficult choice among a number of options: (1) comply with the decision and proceed to destroy their stocks of the virus, (2) refuse to accept the decision as legally binding and continue with open smallpox research, or (3) claim to have destroyed all remaining stocks but continue working with the live virus in the "black" (classified) world. Most experts believe that a resurgent Russia, which appears to view the smallpox virus repository at Vector as a symbol of its importance in world affairs, will not agree to destroy all of its stocks under any circumstances. Thus, a decision by the World Health Assembly in favor of destruction could leave the United States in a political quandary.

How can this diplomatic impasse be avoided? The key issue for U.S. policymakers is to decide how much of a defensive bulwark against smallpox is sufficient, given the low probability but potentially

catastrophic consequences of a deliberate release of the virus, on the one hand, and the safety, security, and political risks associated with continued research with the live virus, on the other. The United States and other countries may well be called on to make this judgment in 2011.

A Grand Bargain

In order to avoid an international confrontation over smallpox virus destruction that would be harmful to all concerned, Washington should be prepared to negotiate a compromise formula that breaks the current deadlock. Such a grand bargain might consist of the following elements:

1. Russia and the United States would agree to reduce the WHO-authorized stocks of the smallpox virus at the CDC and Vector to a small number of representative strains, perhaps 10 at each repository, and to halt all research with the live virus after two effective antiviral drugs have been developed and licensed. Skeptics might argue that destroying most but not all of the virus stocks is like being "a little bit pregnant" and would not satisfy hard-line destructionists. Nevertheless, because Moscow and Washington so far have been entirely unresponsive to the concerns of other countries, the admittedly symbolic action of destroying most of the virus stocks under their control would be a major step toward reconciliation. Destruction would occur in stages, beginning with the strains that are least valuable scientifically, such as the 14 hybrids of the smallpox virus and animal poxviruses (rabbitpox and cowpox) that were prepared by British virologist Keith Dumbell and transferred to the CDC collection.[21] The Advisory Committee on Variola Virus Research found no scientific rationale for further study of the hybrid strains and has recommended repeatedly that they be destroyed.[22] Next on the list for elimination would be roughly 200 strains held at the CDC for which no epidemiological information is available about the clinical effects of the virus in humans. The small number of strains to be retained indefinitely at each repository would be stored under the highest levels of physical security in case there is a scientific need for them in the future. Because most but not all of the virus stocks in Russia and the United States would be eliminated, the standard of evidence required for verification would be less demanding and hence politically more feasible than for complete destruction.

2. All WHO member states would formally acknowledge the threat posed by the potential de novo synthesis of the smallpox virus and reaffirm the existing rules that (a) strictly forbid the chemical synthesis of full-length smallpox virus genomes or their assembly from smaller DNA fragments, (b) prohibit any laboratory outside the two WHO-authorized repositories from holding DNA that comprises more than 20 percent of the smallpox virus genome, (c) ban any genetic engineering of the smallpox virus or the insertion of smallpox viral genes into other poxviruses, (d) require all laboratories outside the two authorized repositories to obtain permission from the WHO to synthesize fragments of smallpox virus DNA longer than 500 base pairs, and (e) authorize the distribution of short fragments of smallpox viral DNA to outside labs that request them through the WHO but permit transfers to third parties only with WHO approval.[23] Under the grand bargain, all member states would pledge to adopt national legislation imposing severe criminal penalties on anyone who breaks these rules and encouraging scientists to report violations to the appropriate national authorities. To facilitate reporting without risk of retaliation, anonymous hotlines or Web sites might be set up for this purpose.

3. To demonstrate the value of smallpox research for the developing world, Russia and the United States would provide assurances that intellectual property rights to drugs or vaccines developed by the research program will be made available free of charge to countries that wish to manufacture them. In addition, Moscow and Washington would contribute to a fund to establish a WHO-controlled stockpile of antiviral drugs for rapid deployment to treat the victims of a smallpox attack, and would increase their allocation of smallpox vaccine to the Global Smallpox Vaccine Reserve maintained by the WHO.[24] Finally, given that smallpox can spread readily from person to person, it is in the interest of all countries to contain an outbreak close to the source, wherever it occurs. To improve the international capacity for prompt detection and containment of smallpox and other epidemic diseases, the United States would offer developing countries technical and financial assistance in setting up national disease surveillance and reporting systems, including diagnostic laboratories, thereby helping them to fulfill the requirements of the revised International Health Regulations.[25]

4. The United States would make medical countermeasures developed under the smallpox research

program available for combating monkeypox, a human disease that closely resembles smallpox but is considerably less lethal and transmissible. Monkeypox is endemic in the Democratic Republic of Congo (DRC) and, in a less virulent form, the rainforest countries of West Africa. Unlike smallpox, it infects rodents and monkeys as well as humans. (In the summer of 2003, a shipment of infected rodents from Ghana destined for the exotic pet trade caused an outbreak of monkeypox in the United States.) Ever since routine vaccination against smallpox ended, the incidence of monkeypox in Africa has risen in parallel with the proportion of the population that is unvaccinated, and the disease now has the potential to establish itself in humans through person-to-person transmission.[26] Unfortunately, mass vaccination against monkeypox in the DRC may not be possible because of the increasing prevalence of HIV/AIDS infection, which suppresses the immune system and renders the smallpox vaccine less effective and potentially life threatening. However, the antiviral drugs developed to treat smallpox should be effective against monkeypox as well. Once these drugs have been licensed, the United States would agree to make them available at a subsidized price or free of charge for the purpose of treating monkeypox in the affected African countries.

5. The World Health Assembly would request the WHO Secretariat to continue making periodic inspections of the smallpox virus repositories in Russia and the United States to ensure that the residual stocks continue to be stored in a safe and highly secure manner.[27]

Such a grand bargain, or a similar negotiating formula, would aim to bridge the gap between the pro-destruction and anti-destruction camps. The proposed foreign assistance programs would generate goodwill throughout the developing world and might be seen as a reasonable quid pro quo for the continued retention of a small number of smallpox viral strains at the two authorized repositories as a hedge against future developments. In any event, creative diplomacy will be needed to break out of the current deadlock and bring the protracted and contentious debate over smallpox virus destruction to a broadly acceptable conclusion.

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Current Status of Smallpox Research

WHO-authorized research with the live smallpox virus over the past decade has yielded a number of medical countermeasures that have made the world better prepared to deal with the potential use of the smallpox virus as a military or terrorist weapon, although a few of the research goals have not yet been met. To date, the program has achieved the following milestones:

- The entire DNA sequences of 45 different strains of the smallpox virus have been determined, as well as the partial DNA sequences of more than 20 additional strains. This sequencing effort has revealed little genetic variation among different strains of the smallpox virus, suggesting that a drug or vaccine that is effective against one strain should work against them all.
- Fast and reliable techniques have been developed for the diagnosis of smallpox infection, including two diagnostic assays for field use based on a genetic detection method (polymerase chain reaction) and two "point-of-care" diagnostic assays based on protein detection.
- An improved version of the standard smallpox vaccine called ACAM 2000, which is manufactured in cell culture rather than in the skin of live calves, has been licensed by the U.S. Food and Drug Administration (FDA). When the supply of ACAM 2000 is combined with the older stocks of smallpox vaccine, the U.S. Strategic National Stockpile now contains enough doses to protect all 300 million Americans.
- A weakened ("attenuated") smallpox vaccine called Modified Vaccinia Ankara (MVA) has been evaluated. This particular strain of the vaccinia virus, developed in Germany in the late 1970s, is incapable of replication and hence is safe to use in the 10 to 15 percent of the population that suffers from atopic dermatitis (eczema), for whom the standard vaccine is contraindicated. A European vaccine manufacturer (Bavarian Nordic) has offered to produce large quantities of MVA if sufficient demand exists. Another attenuated smallpox vaccine, known as LC16m8, has been licensed in Japan and also appears safe and effective.
- Two antiviral drug candidates (CMX-001 and ST-246) have been identified that target different stages of the smallpox virus life cycle and can be given by mouth. Based on data from animal studies, both

compounds appear effective for treating smallpox-infected individuals during the incubation period or early in the course of the illness. Preliminary test-tube experiments also suggest that the two drugs may have synergistic effects when administered together.

- An animal model of smallpox infection has been created in macaque monkeys to assess the efficacy of antiviral drugs and secure regulatory approval from the FDA under the so-called "animal efficacy rule," which permits testing in animal models when clinical trials in humans cannot be performed for ethical or practical reasons. Because smallpox no longer occurs in human populations, the only option for demonstrating the efficacy of new antiviral drugs is the use of an animal model.

Good progress has been made in most of these areas, removing any scientific or regulatory reasons to use live smallpox virus for additional DNA sequencing, the development of diagnostic kits, or the testing of new vaccines. The primary rationale for further work with the live virus is for the testing of antiviral drugs in an animal model of smallpox in order to obtain FDA approval and licensing. The animal efficacy rule requires that the authentic infectious agent, in this case the smallpox virus, be used and that the disease process in the animal model closely resemble that of the human illness.

Because smallpox was a uniquely human affliction, however, simulating it in a nonhuman primate (the cynomolgus macaque) has been extremely difficult. For one thing, monkeys cannot be infected by the natural route of inhaling the smallpox virus into the lungs. Instead, researchers have had to give the animals a massive dose of the virus by intravenous injection, instantaneously producing a systemic infection that seeds the target organs with the virus and gives rise to the characteristic skin rash. Thus, whereas human smallpox had a slow clinical course that began with an incubation period of about two weeks, followed by two to four days of high fever, malaise, and extreme fatigue before the appearance of the skin rash, the illness induced in monkeys is immediate, severe, and lasts only three to six days. Moreover, whereas smallpox in humans had a mortality rate of 10 to 30 percent, the intravenous injection of smallpox virus into monkeys gives rise to a hemorrhagic form of the disease that is almost invariably fatal. Given these discrepancies, U.S. researchers contend that additional work with the live smallpox virus is needed to refine the monkey model (e.g., by reducing the infectious dose and exposing the animals to the virus by a more natural route, such as through the bronchi of the lungs) so that the resulting disease recapitulates the clinical course of human smallpox closely enough to provide a realistic basis for testing the efficacy of antiviral drugs.

Critics of the smallpox-monkey model favor the use of a surrogate virus such as monkeypox, which naturally infects nonhuman primates and is far less dangerous to handle. Recent research also suggests that smallpox infection in monkeys involves a disease process that is physiologically distinct from that of monkeypox in monkeys: in particular, the genes that code for the host's immunological response to the viral infection have different patterns of expression. Because nearly all of the information about how the smallpox virus caused disease in humans dates from the era before the dramatic advances in molecular virology and immunology, it is not known whether smallpox in monkeys or monkeypox in monkeys provides a more accurate model of the disease process that occurred in human smallpox. So far, however, FDA officials have refused to accept the monkeypox-monkey model as the basis for licensing new antiviral drugs for human use under the animal efficacy rule. How this regulatory issue is ultimately resolved could determine the need for continued scientific access to the live smallpox virus over the next few years.

The Checkered History of Smallpox Research at Vector

In 1994 the Russian government unilaterally transferred the smallpox virus stocks under its control to the State Research Center of Virology and Biotechnology "Vector," which subsequently became one of the two WHO-approved repositories. Because of the financial crisis that followed the breakup of the Soviet Union, Vector suffered deep budget cuts and thus lacked the resources to fund its own research with the live smallpox virus. After the World Health Assembly in 1999 authorized the development of medical countermeasures against smallpox, the U.S. Department of Health and Human Services (HHS)'s Biotechnology Engagement Program and the Department of Defense's Cooperative Threat Reduction program channeled funds for smallpox research at Vector through the Moscow-based International Science and Technology Center (ISTC). In addition to financing the renovation of the Russian smallpox repository and laboratory to upgrade its safety and security, the ISTC grants supported several research projects, including work by Sergei N. Shchelkunov and Igor V. Babkin on the genetic characterization of representative smallpox virus strains from the Russian collection, by Evgeny Belanov on the screening of candidate antiviral drugs for activity against the smallpox virus, and by other Vector scientists on the development of new smallpox diagnostic tools.

In 2002, due to lingering concerns about Vector's past involvement in the Soviet biological warfare program, the U.S. Congress sought to increase the transparency of Russian smallpox research by insisting, as a condition of renewed ISTC funding, that U.S. scientists work side-by-side with their Russian colleagues. Although a few U.S. virologists were trained to use Russian biosafety equipment at Vector, the host government never approved the three collaborative research projects that Washington had proposed and in 2004 the ISTC projects became inactive. In May 2005, Vector was classified as a Federal State Research Institution and placed under the control of the Russian Ministry of Health's Federal Inspection Agency for Consumer and Human Welfare Protection. The agency's new head, Gennady G. Onishchenko, fired Vector's director-general, Lev S.

Sandakhchiev, who had promoted extensive scientific collaboration with the West, and replaced him with an old-school scientific bureaucrat named Ilyia G. Drozdov.

Since 2005 the HHS has pressed the Russian Ministry of Health to negotiate an extension of ISTC funding for the three joint smallpox research projects at Vector. But despite the personal intervention of then-HHS Secretary Mike Leavitt, who agreed to drop the condition that U.S. collaborating scientists be resident and to require only periodic visits, approval from Moscow has not been forthcoming. Meanwhile, the transparency of smallpox research at Vector has declined sharply. Russian virologists who formerly interacted freely with their U.S. colleagues have either stopped attending the annual meetings in Geneva of the WHO Advisory Committee on Variola Virus Research or have become far more circumspect.

Now that the safety and security of Vector's smallpox laboratory and repository have been upgraded with U.S. financial support, the Russian government is contributing its own funds to operate the facility. At the most recent meeting of the WHO Advisory Committee in November 2008, the Vector representatives announced that they had resumed screening candidate antiviral drugs against the live smallpox virus after a hiatus of a few years, although they declined to present any data. In addition, Drozdov reported that Vector scientists had transferred a large number of smallpox virus isolates from sealed glass ampoules to unbreakable plastic vials. The purported safety rationale for this operation did not make sense, however, because the process of thawing the samples of frozen virus, opening the glass ampoules, and transferring the contents to plastic vials posed its own set of risks. In another bombshell, Drozdov announced that, after testing the viral isolates in the Russian collection, Vector scientists had thrown out "200 nonviable duplicates," reducing the total number of samples from 891 to 691. The nonviable isolates were destroyed unilaterally, without WHO verification. Thus, Vector's claim to have eliminated 200 samples of the smallpox virus has taken a significant fraction of the Russian collection "off the books" in an unaccountable manner.

In addition to the puzzling new developments at Vector, the U.S. government has lingering suspicions that undeclared stocks of the smallpox virus may exist at a Russian Ministry of Defense facility, the Virology Center of the Scientific-Research Institute of Microbiology, near the city of Sergiev Posad (formerly Zagorsk). During the Soviet period, the Virology Center allegedly mass-produced and weaponized the smallpox virus, and it remains shrouded in secrecy. These unresolved concerns have fostered mistrust and deepened the current chill in U.S.-Russian relations, making it all the more important to enhance transparency and build confidence by reviving the scientific partnership between the two countries. Each side has complementary expertise in smallpox research to bring to the table, as well as unique strains in their respective repositories. Moreover, now that Vector's smallpox laboratory has been upgraded to U.S. government standards, the United States and Russia can become equal partners in research, a status sought for years by the Russian Ministry of Health. To move forward with the collaboration, however, it may be necessary to revise the joint smallpox research projects to take account of the scientific knowledge gained over the past five years. It is to be hoped that the forthcoming Institute of Medicine report on smallpox research will explore new opportunities for U.S.-Russian scientific collaboration in this area.

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ENDNOTES

1. In addition to the deliberate use of the smallpox virus as a military or terrorist weapon, other possible scenarios for a return of the disease include the thawing, due to global warming, of corpses of smallpox victims buried in the Arctic permafrost, infecting individuals who come in contact with the remains, and the evolution of the monkeypox virus to become more transmissible in humans, filling the ecological niche vacated by the eradication of smallpox. Both scenarios are considered extremely unlikely.

2. Natural smallpox infection spread from person to person through virus particles that were shed from lesions in the mouth and throat and were aerosolized by coughing. The airborne virus was then inhaled by others who came into close contact with an infected individual. A primary case infected an average of 3.5 to 6.0 other people. Thus, although it was possible to break the chain of transmission by isolating patients with a visible skin rash and vaccinating all contacts, an outbreak could spread rapidly before containment measures were put in place.

3. The global distribution of laboratories reporting possession of the smallpox virus to the WHO in

1975 was as follows: Africa (5), Americas (18), Southeast Asia (13), Europe (29), eastern Mediterranean (3), and western Pacific (6). Although China did not respond to the WHO survey, samples of the smallpox virus were then held at the Institute for the Control of Drugs and Biological Products in Beijing, bringing the total number of laboratory stocks to 75. See Frank Fenner et al., Smallpox and Its Eradication (Geneva: World Health Organization, 1988), p. 1340.

4. In 1992, the U.S. Congress passed legislation renaming the CDC the "Centers for Disease Control and Prevention."

5. Advisory Committee on Variola Virus Research, World Health Organization (WHO), "Report of the Ninth Meeting, Geneva, Switzerland, 29-30 November 2007," 2008, p. 2. In November 2008, Vector representatives claimed to have reduced the total number of samples from 891 to 691.

6. Ken Alibek with Stephen Handleman, Biohazard: The Chilling True Story of the Largest Biological Weapons Program in the World (New York: Random House, 1999), pp. 107-122.

7. Barton Gellman, "4 Nations Thought to Possess Smallpox: Iraq, N. Korea Named, Two Officials Say," The Washington Post, November 5, 2002, p. A1. In the aftermath of the 2003 Iraq War, the U.S.-led Iraq Survey Group failed to find conclusive evidence that Iraq had possessed stocks of the smallpox virus.

8. Routine vaccination of U.S. civilians against smallpox ended in 1972 but was required for travelers to endemic regions until the late 1970s. In most other countries, vaccination of the general population ended by 1982.

9. Contrary to the general belief that the immunity induced by smallpox vaccination diminishes over time, a recent study found that individuals vaccinated one or more times up to 88 years ago maintained protective antibodies for decades at levels similar to those who had lifetime immunity after surviving smallpox in their youth. These data suggest that multiple or recent vaccinations may not be required to provide immunity to smallpox over a lifetime. See Dennis D. Taub et al., "Immunity From Smallpox Vaccine Persists for Decades: A Longitudinal Study," American Journal of Medicine, Vol. 121, No. 12 (December 2008), pp. 1058-1064. Critics note, however, that the types of immunity needed to protect against smallpox are largely unknown and may not be limited to antibodies.

10. Terrorists might disperse the smallpox virus in the form of an aerosol or cloud of microscopic particles. Popular scenarios in which suicide terrorists infect themselves with the smallpox virus and walk into crowds to spread the infection are implausible because the early stages of the disease involve a high fever and extreme exhaustion, which would keep the terrorists bedridden.

11. Institute of Medicine of the National Academies, Assessment of Future Scientific Needs for Live Smallpox Virus (Washington, DC: National Academies Press, 1999).

12. For details on the operation of the WHO Advisory Committee on Variola Virus Research, see Jonathan B. Tucker, "Preventing the Misuse of Biology: Lessons From the Oversight of Smallpox Virus Research," International Security, Vol. 31, No. 2 (Fall 2006), pp. 116-150.

13. Countries that the United States has accused of pursuing offensive biological warfare programs include China, Iran, North Korea, Russia, and Syria. See Bureau of Verification, Compliance and Implementation, U.S. Department of State, "Adherence to and Compliance With Arms Control, Nonproliferation, and Disarmament Agreements and Commitments," August 2005, pp. 18-31 (unclassified version).

14. Grant McFadden, "Smallpox: An Ancient Disease Enters the Modern Era of Virogenomics," Proceedings of the National Academy of Sciences, Vol. 101, No. 42 (October 19, 2004), p. 14995.

15. WHO, "Smallpox Eradication: Destruction of Variola Virus Stocks: Report by the Secretariat," A61/6, April 14, 2008 (Sixty-first World Health Assembly, provisional agenda item 11.3), p. 4.

16. Daniel G. Gibson et al., "Complete Chemical Synthesis, Assembly, and Cloning of a Mycoplasma genitalium Genome," Science, February 29, 2008, pp. 1215-1220.

17. WHO Advisory Committee on Variola Virus Research, "Report of the Tenth Meeting," Geneva, November 2008, www.who.int/csr/disease/smallpox/research/en/index.html.

18. Alfred D. Steinberg, "Recent Worldwide Research on Animal Pox Viruses," Open Source Center, MITRE Corp., January 2008, p. 3.

19. WHO, "Smallpox Eradication: Destruction of Variola Virus Stocks," WHA60.1, May 18, 2007 (Sixtieth World Health Assembly, agenda item 12.2), p. 2.

20. Board on Global Health, Institute of Medicine, "Statement of Task: Assessment of Future Scientific Needs for Live Smallpox Virus," October 2008.

21. Nell Boyce, "Smallpox Mixes Make a Stir," U.S. News and World Report, January 19, 2004, p. 64.

22. WHO Advisory Committee on Variola Virus Research, "Report of the Fourth Meeting," Geneva, November 20-21, 2002, WHO/CDS/CSR/GAR/2003.5, p. 1; WHO Advisory Committee on Variola Virus Research, "Report of the Fifth Meeting," Geneva, November 4-5, 2003, WHO/CDS/CSR/GAR/2004.15, p. 3; WHO Advisory Committee on Variola Virus Research, "Report of the Sixth Meeting," Geneva, November 4-5, 2004, WHO/CDS/CSR/ARO/2005.4, p. 3.

23. WHO, "WHO Recommendations Concerning the Distribution, Handling and Synthesis of Variola Virus DNA, May 2008," Weekly Epidemiological Record, October 31, 2008, pp. 393-395.

24. The Global Smallpox Vaccine Reserve consists of a permanent reserve in Geneva of at least five million doses, as well as vaccine stocks pledged to the WHO by member countries with national stocks and amounting to at least 200 million doses. The WHO has also recommended that at least two vaccine-production facilities be identified globally with reserve standby capacity for the manufacture of at least 20 million doses. WHO, "Smallpox: Global Smallpox Vaccine Reserve: Report by the Secretariat," A58/9, April 7, 2005 (Fifty-eighth World Health Assembly, provisional agenda item 13.6).

25. WHO, International Health Regulations (2005), www.who.int/csr/ihr/en/.

26. Anne W. Rimoin et al., "Endemic Human Monkeypox, Democratic Republic of Congo, 2001-2004," Emerging Infectious Diseases, Vol. 13, No. 6 (June 2007), pp. 934-937.

27. The WHO inspected the smallpox repositories at the CDC and Vector in 2002 and 2005. The next visits are scheduled for the first half of 2009.

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