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Global Governance of "Contentious" Science: The Case of the World Health Organization's Oversight of Small Pox Virus Research

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Jonathan B. Tucker and Stacy M. Okutani

Introduction

A major challenge facing efforts to prevent the spread of biological weapons to "rogue" states and terrorist organizations is the dual-use nature of biotechnology: the fact that the same technical know-how and equipment involved in the peaceful development and production of vaccines and other commercial products can be diverted into offensive applications. This "dual-use dilemma" carries over into basic research in the life sciences.[1] When microbiologists publish research papers that elucidate the process of infection, describe the molecular basis of pathogenesis, or explore the physiological action of toxins, they add to the existing body of knowledge and contribute to the development of medical therapies. Yet countries seeking biological weapons could utilize the same information to devise more deadly infectious agents and methods of delivery. Examples of such dual-use research include the unexpected discovery that inserting the gene for an immune-system protein renders mousepox virus more lethal and vaccine-resistant in mice; the identification of a smallpox protein that contributes to the virulence of the disease in humans; and the synthesis of poliovirus in the test tube.[2]

The most serious threat of misuse of this information does not arise from terrorist organizations, which have limited scientific expertise, but rather from scientists employed by sophisticated, well-funded national BW programs. These individuals keep up with the scientific literature and are capable of exploiting basic research findings to pursue weapons-related developments. It is therefore important to address these

[1] G. Kwik, et al., "Biosecurity: Responsible Stewardship of Bioscience in an Age of Catastrophic Terrorism," *Biosecurity and Bioterrorism*, vol. 1, no. 1 (2003), pp. 1-9.

[2] R. J. Jackson, et al., "Expression of Mouse Interleukin-4 by a Recombinant Ectromelia Virus Suppresses Cytolytic Lymphocyte Responses and Overcomes Genetic Resistance to Mousepox," *Journal of Virology*, vol. 75 (2001), pp. 1205-1210; Ariella M. Rosengard, et al., "Variola Virus Immune Evasion Design: Expression of a Highly Efficient Inhibitor of Human Complement," *Proceedings of the National Academy of Sciences*, vol. 99, no. 13 (June 25, 2002), pp. 8808-8813; J. Cello, et al., "Chemical Synthesis of Poliovirus cDNA: Generation of Infectious Virus in the Absence of Natural Template," *Science*, vol. 297 (2002), pp. 1016-1018.

biological security concerns in a way that does not cause serious harm to the scientific enterprise.[3]

In October 2003, an expert committee under the auspices of the U.S. National Academy of Sciences, chaired by Prof. Gerald R. Fink of MIT, published a report acknowledging the potential for misuse of certain basic research findings in the life sciences by proliferators and terrorists, and proposing a system for the voluntary review and self-regulation by the U.S. scientific community of seven types of "experiments of concern."[4] In response to the Fink Committee report, the Bush administration announced the creation of a National Science Advisory Board on Biosecurity (NSABB) to advise all Federal departments and agencies that conduct or support biological research that could be misdirected to threaten public health or national security.[5]

Because bioscience is an international enterprise, any system designed exclusively to regulate U.S. scientists or scientific journals will not be effective. The Fink Committee report acknowledged this problem, noting that "any serious attempt to reduce the risks associated with biotechnology must ultimately be international in scope, because the technologies that could be misused are available and being developed throughout the globe."[6] To address this problem, the committee recommended the creation of an "International Forum on Biosecurity" to develop harmonized national, regional, and international biosecurity measures. Yet the report did not suggest a strategy for creating a global scientific oversight system or how it might operate.

In an early attempt to grapple with the international dimension of overseeing dual-use research in the life sciences, Dr. Gerald Epstein, a former deputy director for national security in the White House Office of Science and Technology Policy, proposed in 2001 the creation of an "international advisory group" to develop and recommend guidelines for national regulatory authorities and the scientific community at large. Epstein noted, however, that without an international treaty through which individual nations voluntarily subject themselves to the group's authority, its legitimacy and

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[3] Raymond A. Zilinskas and Jonathan B. Tucker, "Limiting the Contribution of the Open Scientific Literature to the Biological Weapons Threat," *Journal of Homeland Security*, December 2002, <http://www.homelandsecurity.org/journal/Articles/Tucker.html>

[4] National Research Council, National Academy of Sciences, *Biotechnology Research in an Age of Terrorism: Confronting the Dual-Use Dilemma* (Washington, DC: National Academies Press, 2003).

[5] "HHS Will Lead Government-Wide Effort to Enhance Biosecurity in 'Dual Use' Research," *HHS News* (Press Release), March 4, 2004.

[6] National Research Council, *Biotechnology Research in an Age of Terrorism*, p. 12.

influence would depend on the extent to which its members were respected by their scientific peers.[7] More recently, a policy analysis group at the University of Maryland developed a proposal for the multi-tiered oversight of "high-consequence" research in the biosciences. This proposal calls for the creation of a global standard-setting and review body called the "International Pathogens Research Agency," which would define research activities subject to oversight and oversee the implementation of internationally agreed rules by national governments.[8]

At present, no multilateral organization oversees "contentious" research in the life sciences. Nevertheless, an international scientific committee with more limited scope—the oversight of research with live smallpox virus—currently exists under the auspices of the World Health Organization (WHO). Since its inception in 1999, this body, known as the WHO Advisory Committee on Variola Virus Research ("variola" is the scientific name for smallpox) has monitored studies aimed at developing countermeasures against the deliberate use of smallpox as a military or terrorist weapon. Accordingly, the five-year track record of this committee provides an empirical basis for assessing the feasibility of a broader oversight mechanism to ensure the safety and defensive orientation of research with the most dangerous pathogens.

Smallpox: Eradication and Resurgent Threat

Smallpox, a devastating scourge that claimed hundreds of millions of lives over the course of human history, was eradicated in 1977 thanks to a decade-long global vaccination campaign led by the World Health Organization (WHO). An international bureaucracy based in Geneva, Switzerland, WHO does not conduct laboratory research but instead coordinates public health activities by member states and establishes international forums where technical experts can discuss scientific and policy issues and reach consensus on a plan of action. As an international scientific organization, WHO enjoys considerable prestige and credibility; it is widely seen as politically neutral and

[7] Gerald L. Epstein, "Controlling Biological Warfare Threats: Resolving Potential Tensions Among the Research Community, Industry, and the National Security Community," *Critical Reviews in Microbiology*, vol. 27, no. 4 (2001), pp. 321-354.
[8] John Steinbruner, Elisa Harris, Nancy Gallagher, and Stacy Gunther, "Controlling Dangerous Pathogens: A Prototype Protective Oversight System" (updated Sept. 2003), <http://www.cissm.umd.edu/documents/pathogensmonograph.pdf> See also, John D. Steinbruner and Elisa D. Harris, "Controlling Dangerous Pathogens," *Issues in Science and Technology*, Spring 2003, pp. 47-54.

serving the interests of all member states. For this reason, WHO officials can gain access to sensitive facilities or activities that would be denied to representatives of foreign governments.

In the early 1980s, countries throughout the world responded to the eradication of smallpox by halting the routine vaccination of their populations against the disease, saving billions of dollars that could be redirected to other public health challenges. In 1992, however, a senior Soviet defector told the CIA that Moscow had developed smallpox into a biological warfare agent and then gone on to mass-produce and stockpile the virus in multi-ton quantities.[9] This revelation, combined with the progressive loss of population immunity, reductions in vaccine stocks, and lack of physician familiarity with the disease all combined to increase the threat of smallpox as a biological weapon.[10]

In view of the epidemic potential of smallpox and its average lethality of 30 percent, the virus heads the CDC's list of the most dangerous bioterrorist threat agents.[11] Although the threat of bioterrorism involving smallpox is real, it has been widely exaggerated: both the biology of the virus and the historical record argue against a scenario in which a smallpox epidemic would spread like wildfire around the world, as portrayed in the well-known "Dark Winter" exercise.[12] Smallpox appears to be about as contagious as SARS, and its control would be greatly facilitated by the solid vaccine protection of health-care workers and first responders, a readily recognizable rash, and the potential for effective antiviral drug therapy and prophylaxis.

In the mid-1970s, several years before smallpox was eradicated from the globe, WHO began taking steps to ensure that the disease would not reemerge as the result of an accidental release from a research laboratory. Given WHO's role in leading the global eradication campaign, the organization claimed responsibility for overseeing all scientific research on smallpox. During the 1970s, WHO established safety guidelines for work

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[9] Ken Alibek with Stephen Handelman, *Biohazard* (New York: Random House, 1999).
[10] For an account of the eradication of smallpox and its reemergence as a bioterrorist threat, see Jonathan B. Tucker, *Scourge: The Once and Future Threat of Smallpox* (New York: Atlantic Monthly Press, 2001).
[11] Lisa D. Rotz, Ali S. Khan, Scott R. Lillibridge, Stephen M. Ostroff, and James M. Hughes, "Public Health Assessment of Potential Biological Terrorism Agents," *Emerging Infectious Diseases*, vol. 8, no. 2, February 2002, <www.cdc.gov/ncidod/eid/vol8no2/01-0164.htm>
[12] Tara O'Toole and Thomas Inglesby, "Shining Light on Dark Winter," *Biodefense Quarterly*, vol. 3, no. 2 (Autumn 2001), pp. 1-3, 8-9.

with the virus, identified and consolidated the number of laboratories holding collections of smallpox isolates, and sought to regulate all future activities involving the live virus.[13]

In 1979, the WHO Global Commission for the Certification of Smallpox Eradication issued a final report confirming that smallpox had been eradicated from the planet. This report made nineteen recommendations for the post-eradication era, including that WHO maintain no more than four collaborating centers for diagnostic work and scientific research on smallpox virus under conditions of maximum biocontainment (Biosafety Level 4, or BSL-4). Each center would report annually to WHO and would be inspected periodically. WHO also requested all other laboratories possessing stocks of smallpox virus to destroy the specimens in their possession or transfer them to one of the approved collaborating centers.

In 1981, former members of the Global Commission gathered to discuss the implementation of the post-eradication policies. The agenda included assuring that the stockpile of smallpox vaccine was properly stored and maintained, archiving the records of the eradication program, and assessing the threat to international public health posed by limited outbreaks of a related viral disease, human monkeypox. The Director-General of WHO subsequently appointed this group as the Committee on Orthopoxvirus Infections, under the chairmanship of Frank Fenner, a poxvirologist from Australia.[14] After 1988, the committee no longer met on an annual basis and became an Ad Hoc Committee that convened only when necessary to address specific policy issues.

By 1984, the number of WHO smallpox collaborating centers had been reduced to two: the Institute for Viral Preparations in Moscow, which held about 120 isolates of the virus, and the U.S. Centers for Disease Control and Prevention (CDC) in Atlanta, which held about 300 samples. In 1994, the Russian government secretly transferred the strain collection at the Moscow institute to the State Research Center for Virology and Biotechnology "Vector" in Koltsovo, Siberia, notifying WHO only after the transfer had occurred. Although this action violated WHO regulations, nothing could be done after the fact. Also in 1994, the Ad Hoc Committee on Orthopoxvirus Infections issued guidelines for handling smallpox DNA, which is not infectious. The committee ruled that "clones" (multiple copies) of pieces of the viral DNA could be distributed on request to

[13] Frank Fenner, et al., *Smallpox and Its Eradication* (Geneva, Switzerland: World Health Organization, 1988), pp. 1273-1276.
[14] Ibid., p. 1285.

legitimate research laboratories but not shared with third parties, and that no laboratory other than the two official WHO repositories could hold more than 20 percent of the viral genome, or full complement of DNA. Furthermore, smallpox DNA could not be inserted into vaccinia, the virus used as the smallpox vaccine, or into other animal poxviruses.[15]

The Ad Hoc Committee also recommended that for safety reasons, the stocks of live smallpox virus held at the CDC and Vector should be destroyed in 1996, after the DNA sequences of representative isolates of the virus had been determined. A series of delays in the date of destruction ensued, however. In May 1996, the World Health Assembly, the annual policymaking meeting of WHO member states, agreed to set June 30, 1999 as the date for destroying the smallpox virus stocks held at the CDC and Vector. But defector reports of Soviet large-scale production of smallpox virus as a biological weapon during the 1970s and '80s, along with circumstantial evidence that undeclared stocks of the virus might exist elsewhere in Russia and in other countries such as North Korea, Iraq, and Iran, increased concerns about the potential threat posed by smallpox.[16] Accordingly, a U.S. interagency working group recommended postponing destruction of the virus stocks until the end of 2002 to permit the development of improved defenses.

In making this decision, the U.S. government drew on a report by the Institute of Medicine of the National Academy of Sciences recommending an agenda for research with live smallpox virus, including the development of diagnostic tools, therapeutic drugs, and a safer vaccine.[17] On May 22, 1999, the World Health Assembly followed the U.S. lead by adopting a resolution authorizing the "temporary retention" of the smallpox virus stocks at the CDC and Vector until the end of 2002, to permit "further international research into antiviral agents and improved vaccines" and "high-priority investigations of the genetic structure and pathogenesis of smallpox," while building an international consensus for destruction of the viral stocks.[18]

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[15] World Health Organization, "Report of the Meeting of the *Ad Hoc* Committee on Orthopoxvirus Infections," Geneva, September 9, 1994, WHO/CDS/BVI/94.3, p. 8.
[16] Barton Gellman, "4 Nations Thought To Possess Smallpox: Iraq, N. Korea Named, Two Officials Say," *Washington Post*, November 5, 2002, p. A1.
[17] Institute of Medicine, National Academy of Sciences, *Assessment of Future Scientific Needs for Live Variola Virus* (Washington, D.C.: National Academy Press, 1999).
[18] Judith Miller and Lawrence K. Altman, "Health Panel Recommends a Reprieve for Smallpox," *New York Times*, May 22, 1999, p. 3.

The World Health Assembly also decided that all research with live smallpox virus would be conducted "in an open and transparent manner only with the agreement and under the control of WHO." To this end, the assembly mandated the creation of a new WHO expert group called the Advisory Committee on Variola Virus Research. According to its mandate, this new body would decide what types of research should be done with live smallpox virus and approve and oversee all such projects; devise a mechanism for reporting the research results to all WHO member states; and recommend to the World Health Assembly when it would be feasible to destroy the virus stocks after completion of the agreed research agenda. Although WHO would oversee all research with live smallpox virus, member states would fund the work through voluntary contributions made outside the organization's regular budget.[19] In addition, WHO would conduct periodic inspections of the smallpox repositories and laboratories at CDC and Vector to ensure a safe working environment and the secure containment of the virus stocks.

The World Health Assembly resolution stated that the smallpox research agenda was to be time-limited and completed as soon as possible, with destruction of the virus stocks at CDC and Vector foreseen by the end of 2002. According to D. A. Henderson, however, the U.S. government viewed the scientific review process as a vehicle to forestall destruction of the smallpox virus stocks at CDC, with the ultimate goal of retaining them indefinitely.[20]

Establishment of the WHO Advisory Committee

Because WHO had not previously been involved in smallpox research, the WHO Secretariat had to create the new oversight committee from scratch. Dr. Lindsey Martinez and Dr. David Heymann of WHO recruited Dr. Riccardo Wittek, a poxvirologist from the nearby University of Lausanne, to set up the committee. The Swiss government agreed to pay part of Wittek's salary so that he could devote 25 percent of his time to selecting the committee members and developing a process for reviewing smallpox research proposals. In choosing the members of the advisory committee, Dr. Wittek sought the participation of the world's leading poxvirologists, while also ensuring a broad geographical distribution as required by WHO rules. In the end, sixteen

[19] World Health Organization, "Smallpox Eradication: WHO Advisory Committee on Variola Virus Research," *Weekly Epidemiological Record*, vol. 75, no. 6 (February 11, 2000), pp. 45-48.
[20] Tucker/Okutani interview with D. A. Henderson, Baltimore, April 27, 2004.

scientists from all six WHO regions were selected as voting members. To provide additional expertise, ten poxvirologists from several countries were named advisers to the committee.[21]

At the annual meetings of the WHO Advisory Committee, the participants hear presentations by scientists working with live smallpox virus, discuss next steps, and make recommendations. So far, the advisory committee has made all of its decisions by consensus. The committee reports its findings directly to the WHO Director-General, who in turn issues a report to the World Health Assembly. To ensure transparency, abstracts of smallpox research projects and detailed minutes of Advisory Committee meetings are posted on the WHO web site.[22] These reports are far more detailed than those usually submitted to member states. Funding for the annual meetings is provided outside the regular WHO budget through a donation of $250,000 by the Swiss government.[23] In addition, the United States pays for nearly all research with live smallpox virus at CDC and Vector.

The first meeting of the WHO Advisory Committee on December 6-9, 1999, included an extensive discussion of the merits of destroying the smallpox virus stocks or retaining them for additional research. Like the Ad Hoc Committee before it, the Advisory Committee was divided into "destructionist" and "retentionist" camps, which continued the earlier debate.[24] Four veterans of the smallpox eradication campaign who had witnessed the devastation caused by the virus—D. A. Henderson of the United States, Kalyan Bannerjee of India, Isao Arita of Japan, and Hermann Schatzmayr of Brazil—pressed for limiting the amount of work with the live virus and setting a date-certain for destruction. But other members of the committee felt that given the possible threat of bioterrorism with smallpox, it was prudent to conduct additional defensive research and development.

Both camps finally agreed on a time-limited research program with the live virus that focused on defined priority areas and was subject to careful WHO oversight.[25] The Advisory Committee identified several priority areas requiring access to live smallpox

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[21] Okutani interview with Riccardo Wittek, Lausanne, Switzerland, May 7, 2004.
[22] For WHO smallpox research abstracts and reports, look under "Governance" at www.who.org
[23] Tucker/Okutani interview with Ray Arthur, CDC, July 12, 2004.
[24] Ibid.
[25] World Health Organization, "Future Research on Smallpox Virus Recommended," Press Release WHO/77, December 10, 1999.

virus: (1) determining the full or partial DNA sequences of additional isolates; (2) validating improved diagnostic tests; (3) screening antiviral drugs to identify those suitable for treating smallpox; (4) developing and producing monoclonal antibodies to treat the disease; (5) developing a safer vaccine, although this work would not necessarily require access to smallpox virus; and (6) creating a model of smallpox in a non-human primate to facilitate testing of antiviral drugs, vaccines, and diagnostics.[26]

Because the smallpox work program was limited to practical, near-term studies, the Advisory Committee rejected some areas of research as overly ambitious or open-ended. For example, a proposal for a broad-based program of drug development, including biopharmaceuticals such as interferons and chemokines, was rejected because such research would extend beyond the end-2002 deadline. Instead, the Advisory Committee decided that the development program should focus on previously identified drug candidates. Similarly, when some members of the committee argued for a program of basic research on smallpox virus, others urged that such work be given a low priority because it would require scarce space in the maximum-containment laboratory at CDC. It was ultimately agreed that some basic research would be conducted in parallel with applied work, but with specific benchmarks and defined endpoints.[27] Moreover, many types of basic research did not require access to live smallpox virus and could be conducted with noninfectious viral DNA or proteins expressed from it.

Although all research with live smallpox virus must take place in the BSL-4 laboratories at CDC and Vector, the work may be conducted by outside scientists who have been authorized by WHO. For example, teams from the U.S. Army Medical Research Institute of Infectious Diseases (USAMRIID) at Fort Detrick, Maryland, and the Defence Science and Technology Laboratory (DSTL) at Porton Down, England, have conducted research with the live virus at CDC.

Operation of the WHO Advisory Committee

To review all smallpox research proposals prior to submission to national funding agencies, WHO staff selected a Scientific Subcommittee made up of five practicing

[26] World Health Organization, WHO Advisory Committee on Variola Virus Research, "Report of a WHO Meeting," Geneva, 6-9 December 1999, WHO/CDS/CSR/2000.1.
[27] D. A. Henderson, "Meeting of the WHO Variola Research Committee," December 6-9, 1999, unofficial memo for the record.

poxvirologists, including one each from CDC and Vector. This structure was designed to permit a rapid turn-around of research proposals, while ensuring consistency with WHO priorities and time constraints. The initial members of the Scientific Subcommittee were Dr. Brian Mahy (CDC, USA), Dr. Sergei N. Shchelkunov (Vector, Russia), Dr. Robert Drillien (INSERM, France), Dr. Geoffrey L. Smith (Imperial College of Medicine, UK), and Dr. Robert Snoeck (Katholieke Universiteit Leuven, Belgium).

The review of smallpox research proposals is straightforward and based on scientific merit and biosafety requirements. Members of the Scientific Subcommittee write comments on each proposal, after which Dr. Wittek seeks clarifications and prepares a consensus report with specific recommendations.[28] Overall, the peer-review process has helped researchers to remain focused on the agreed goals and timeframe of the smallpox research program. According to CDC poxvirologist Joseph Esposito, "I'm impressed by how carefully the issues are vetted—you can sit there for an hour talking over one small point. But most of the time the juice is worth the squeeze."[29]

During the second meeting of the WHO Advisory Committee on February 15-16, 2001, members received an update of progress in the various research areas.[30] Seven months later, the terrorist attacks against New York and Washington on September 11, 2001, and the subsequent mailings of anthrax bacterial spores, heightened the perception of a potential bioterrorist threat involving smallpox. Three months after the events of 9/11, the WHO Advisory Committee held its third meeting on December 3-4, 2001. By now it was clear that although important progress in smallpox research had been achieved, "significant components" of the agreed program would not be completed by the end of 2002. The Advisory Committee therefore recommended another delay in destroying the viral stocks.[31]

When the World Health Assembly convened in May 2002, the lingering impact of 9/11 caused many countries that had previously sought to destroy the smallpox virus stocks to support ongoing defensive research. Accordingly, WHO members agreed to extend the research program beyond the December 2002 deadline, without setting a

[28] Okutani interview with Riccardo Wittek, Lausanne, Switzerland, May 7, 2004.
[29] Tucker interview with Joseph Esposito, CDC, July 13, 2004.
[30] World Health Organization, WHO Advisory Committee on Variola Virus Research, "Report of the Second Meeting," Geneva, 15-16 February 2001, WHO/CDS/CSR/EDC/2001.17.
[31] World Health Organization, WHO Advisory Committee on Variola Virus Research, "Report of the Third Meeting," Geneva, 3-4 December 2001, WHO/CDS/CSR/GAR/2002.3.

specific date for destruction. Instead, retention of the virus stocks was left open-ended, pending completion of the full set of research objectives. At the same time, the World Health Assembly reaffirmed the mandate of the WHO Advisory Committee to review, approve, and monitor all research with live smallpox virus at CDC and Vector, while ensuring that the approved projects remained "outcome-focused and time-limited."[32]

At its fourth meeting on November 20-21, 2002, the WHO Advisory Committee discussed a number of biosafety issues related to smallpox research, including the simultaneous handling of smallpox and related poxviruses within the same maximum-containment lab; the insertion into smallpox virus of "reporter" genes, such as one encoding a green fluorescent protein; the expression of smallpox genes in other poxviruses; and the distribution of smallpox DNA and its synthesis in the test tube. Although the research guidelines established in 1994 by the Ad Hoc Committee on Orthpoxvirus Infections had banned all such activities, the WHO Advisory Committee recognized that these rules "were now open to challenge because of the technological advances that have been made since the existing guidelines were first introduced." To advise the WHO on these matters, the Advisory Committee formed a Technical Subcommittee of experts in molecular biology who would review the issues and develop revised guidelines for research with smallpox virus.[33]

At the fifth meeting of the WHO Advisory Committee on November 4-5, 2003, the Technical Subcommittee gave its opinion on the four unresolved policy issues. After lengthy discussion, the Advisory Committee recommended that these issues and the views of committee members be referred to the WHO Biosafety Advisory Group to determine the appropriate level of biocontainment for various experiments. The four issues would then be referred to the Ad Hoc Committee on Orthopoxvirus Infections for final adjudication.[34]

What is the current status of the smallpox research program? A group of poxvirologists recently estimated that the development of two anti-smallpox drugs that work by different mechanisms will require an investment of seven to ten years and $1.5

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[32] Fifty-Fifth World Health Assembly, Agenda Item 13.16, "Smallpox Eradication: Destruction of *Variola virus* Stocks," Ninth Plenary Meeting, WHA55.15, May 18, 2002.
[33] WHO Advisory Committee on Variola Virus Research, "Report of the Fourth Meeting," Geneva, 20-21 November 2002, WHO/CDS/CSR/GAR/2003.5, p. 6.
[34] WHO Advisory Committee on Variola Virus Research, "Report of the Fifth Meeting," Geneva, 4-5 November 2003, pp. 7-8.

to $2.5 billion.[35] An animal model of smallpox has already been developed, and one of the two required antiviral drugs (cidofovir) is already licensed, although an effort is now being made to develop an orally available form. Once the stated objectives of the smallpox research program have been achieved, will the WHO Advisory Committee recommend destruction of the virus stocks? According to Dr. James Hughes, director of CDC's National Center for Infectious Diseases (NCID), "That is the expectation. We'll see where we are when that day comes."[36]

CDC virologist James LeDuc believes that it is not too early to begin preparing for the "endgame" of the smallpox research program with respect to technical issues surrounding the possible destruction of the smallpox virus stocks, but he is realistic about the political feasibility of destruction. "There are two separate universes: one is the science, which is eventually going to be completed, and the other is politics," he says. "I don't think the politics are ever going to let us destroy anything, at least in the current environment."[37]

Controversial Policy Issues

Three issues addressed by the WHO Advisory Committee have been particularly contentious, raising important issues of scientific oversight.

Destruction of Chimeric Viruses

During the 1970s and early 1980s, British virologist Keith Dumbell created "chimeric" poxviruses containing a mixture of genetic material by infecting cells simultaneously with smallpox virus and an animal poxvirus, such as rabbitpox or cowpox. When the British strain collection was transferred to the CDC, the chimeric poxviruses were included. Vials containing these viruses have been stored in a liquid-nitrogen freezer at CDC for decades and have not been opened even to test the cultures for viability.

At its meeting in 2002, the WHO Advisory Committee agreed by consensus to recommend destruction of the chimeras, although copies of the viral DNA could be

[35] Stephen B. Harrison et al., "Discovery of Antivirals Against Smallpox," *Proceedings of the National Academy of Sciences*, vol. 101, no. 31 (August 3, 2004), p. 11188.
[36] Tucker/Okutani interview with James Hughes, CDC, July 12, 2004.
[37] Tucker/Okutani interview with James LeDuc, CDC, September 16, 2004.

preserved. The reason for this decision was that because improved techniques have since been developed for determining the function of particular genes, there would be no scientific merit in studying Dumbell's chimeras. Reducing the size of the smallpox strain collection would also be consistent with the Advisory Committee's mandate to help build an international consensus for destruction of the virus stocks.

U.S. government officials, however, balked at the WHO Advisory Committee's recommendation. A spokesperson for the U.S. Department of Health and Human Services, which oversees CDC, said that the WHO committee was only "part of the process" and that the United States viewed the chimeric viruses as an integral part of the collection of smallpox virus isolates that the World Health Assembly had decided should be retained for research. This controversy also raised new questions about the international legal status of the virus stocks held at CDC and Vector.[38] Are the two repository countries holding the stocks in trust for the world community? Do the original owners have some residual rights over the fate of the stocks? Do the CDC and Vector derive special legal authority from their physical control of the virus collections?

CDC scientists Joseph Esposito and James LeDuc contend that the chimeras retain some scientific value. Two types of experiments might be performed with them: testing antiviral drugs against the chimeric viruses, which may respond differently because they are recombinants; and extracting DNA from the chimeras in order to test new diagnostic methods to see how well they recognize the insertion of foreign genes into smallpox virus. CDC plans to do both experiments, after which the chimeras could potentially be destroyed.[39] There are political obstacles, however. "We can't just go in and destroy them—we first need approval from our government," LeDuc explained. "Right now that's not forthcoming, so we find ourselves in a bit of a difficult situation."[40]

At its fifth meeting in 2003, the WHO Advisory Committee expressed impatience with the CDC's failure to destroy the chimeras and suggested that "WHO should approach the responsible authorities of the collaborating centres to implement the recommendations concerning the destruction of these virus isolates."[41] The success of

[38] Nell Boyce, "Smallpox Mixes Make a Stir," *U.S. News and World Report*, January 19, 2004.
[39] Tucker interview with Joseph Esposito, July 13, 2004; Tucker/Okutani interview with James LeDuc, September 16, 2004.
[40] Tucker/Okutani interview with James LeDuc, CDC, September 16, 2004.
[41] WHO Advisory Committee on Variola Virus Research, "Report of the Fifth Meeting," Geneva, 4-5 November 2003, p. 3.

such an effort seems doubtful, however, because NCID director Hughes claims that he does not have the authority to destroy the stocks. "At the end of the day, any decision to destroy anything will have to be made at a higher level," he said.[42] Because the United States government as a whole is a member of WHO, any action affecting the smallpox virus collection is a political-scientific decision that will have to be made through the interagency policy-making process.

Senior Bush administration officials oppose the destruction of the chimeric viruses on the grounds that it could become a "slippery slope." If the United States were to agree to destroy a portion of the CDC collection, they argue, that precedent would lead to a renewed debate each year over whether or not to destroy an additional tranche. Indeed, WHO Advisory Committee members Bannerjee and Schatzmayr argued early on for destroying all but six representative isolates. According to White House officials, the U.S. government will be prepared to destroy the smallpox virus stocks only when the biodefense research agenda has been completed and the virus is no longer needed. Until that goal has been achieved, reducing the size of the CDC collection "will not make the world any safer."[43]

Insertion of a Reporter Gene Into Smallpox Virus

The second controversy concerns a proposal by Dr. John Huggins of USAMRIID to insert into smallpox virus a foreign "reporter" gene that codes for a green fluorescent protein (GFP) to permit rapid detection of viral replication in infected cells. Because this technique provides a rapid, non-subjective readout of drug effect, it would facilitate the screening of smallpox-killing drugs. Nevertheless, the GFP gene-insertion experiment is the only smallpox research proposal that the Advisory Committee has sent back to the investigators for revision. One reason is that the research guidelines established by the Ad Hoc Committee on Orthopoxvirus Infections in 1994 prohibit any genetic manipulation of the smallpox virus.

The insertion into viruses of reporter genes such as GFP is now a standard technique for the rapid screening of antiviral drugs to assess their effectiveness, and it would clearly facilitate the process of developing new drugs to treat smallpox. Even so, the proposal has aroused biosafety concerns. At its third meeting in 2001, the WHO

[42] Tucker/Okutani interview with James Hughes, CDC, July 12, 2004.
[43] Tucker/Okutani interview with U.S. government official, May 31, 2004.

Advisory Committee agreed that "an extensive and reasoned risk analysis was needed" for the GFP gene-insertion proposal and requested an advisory opinion from WHO's Biosafety Advisory Group.[44] In 2003, the Advisory Committee concluded that the reporter-gene experiment should be allowed if compelling reasons exist for generating such recombinants and risk analysis determines that insertion of the marker gene would not alter the biological properties of the smallpox virus.[45] To date, GFP has been introduced into several viruses without affecting their virulence, and no evidence indicates that the insertion of a single marker gene into smallpox would increase the ability of the virus to cause disease.

On a more philosophical level, however, some members of the Advisory Committee expressed concern that allowing any genetic engineering of smallpox virus, however benign the intended purpose, could open the door to more dangerous manipulations. Accordingly, the committee was forced to balance the scientific benefits of the experiments against the political liabilities. At the fifth meeting of the Advisory Committee, the Technical Subcommittee recommended approving the insertion of the GFP gene into smallpox virus but urged that all materials and stocks of recombinant virus be destroyed at the end of the experiment.[46] According to CDC virologist Brian Mahy, the Advisory Committee believes that the insertion of a reporter gene into smallpox virus is a special case that would not set a broader precedent.[47]

Insertion of Smallpox Genes into Other Poxviruses

A still more contentious issue involves the proposed insertion of smallpox genes into animal poxviruses. For example, some scientists want to take genes that might serve as antiviral drug targets and insert them into vaccinia, a relatively benign poxvirus that serves as the vaccine against smallpox. Advocates of this proposal argue that the introduction of individual smallpox genes into vaccinia could be useful for testing antiviral drugs and monoclonal antibodies in small-animal models without the risks of

[44] World Health Organization, WHO Advisory Committee on Variola Virus Research, "Report of the Third Meeting," Geneva, 3-4 December 2001, WHO/CDS/CSR/GAR/2002.3.
[45] Nell Boyce, "Smallpox Mixes Make a Stir," *U.S. News and World Report*, January 19, 2004.
[46] WHO Advisory Committee on Variola Virus Research, "Report of the Fourth Meeting," Geneva, 20-21 November 2002, WHO/CDS/CSR/GAR/2003.5.
[47] Tucker/Okutani interview with Brian Mahy, CDC, July 12, 2004.

working with intact smallpox virus.[48] Such genetic-engineering experiments are controversial, however, because they have the potential to be misused for offensive purposes and could set a dangerous precedent. The CDC's LeDuc believes that although each experiment should be assessed on its own merits, the default policy should be not to use smallpox genes for this type of research. He notes that other poxviruses are much safer to work with and do not entail the political sensitivities associated with smallpox.[49]

At the fifth meeting of the WHO Advisory Committee, the Technical Subcommittee recommended that the insertion of smallpox genes into other poxviruses be permitted if a detailed risk analysis demonstrates that expression of the gene is unlikely to alter the biological properties of the recombinant virus. Furthermore, only single genes would be inserted, and all such experiments would be performed at a high level of containment (BSL-3). Some members of the Advisory Committee disagreed with this recommendation, however, on the grounds that "the full scope of the issues under consideration was felt to be beyond the expertise of members of the technical subcommittee alone."[50] The issue was therefore referred to the reconvened Ad Hoc Committee on Orthopoxvirus Infections for a final decision.

Limits to the Authority of the Advisory Committee

No decisions by the WHO are legally binding (with the sole exception of the International Health Regulations). The organization also lacks formal enforcement powers and cannot compel member states to carry out its decisions. As a result, the Advisory Committee's authority to oversee smallpox research rests on the politically binding 1999 resolution of the World Health Assembly that created the committee and the 2002 resolution extending its mandate, both of which were endorsed by consensus. The recommendations of the WHO Advisory Committee carry a certain authority and moral weight because they are made by recognized experts on the basis of objective scientific and safety criteria. In the case of the United States and Russia, political self-interest also plays a role: without the international legitimacy provided by the WHO

[48] Harrison et al., "Discovery of Antivirals Against Smallpox," p. 11190; Tucker/Okutani interview with Richard W. Moyer, University of Florida, May 19, 2004.
[49] Tucker/Okutani interview with James LeDuc, CDC, September 16, 2004.
[50] WHO Advisory Committee on Variola Virus Research, "Report of the Fifth Meeting," Geneva, 4-5 November 2003, p. 8.

Advisory Committee, the World Health Assembly would not have authorized retention of the smallpox virus stocks at CDC and Vector for biodefense research.

In general, the record of voluntary cooperation with WHO resolutions has been good. During the 1970s, most countries complied with WHO's request either to destroy their smallpox virus stocks or transfer them to a designated collaborating center. A prominent exception, however, was the Soviet Union and then Russia, which violated WHO rules by weaponizing smallpox during the 1970s and transferring its smallpox virus collection from Moscow to Siberia in 1994 without prior notification. Russia is also suspected of maintaining stocks of smallpox virus outside the official WHO repository, possibly at a Ministry of Defense facility near the city of Sergiev Posad.

Although compliance with WHO decisions is generally expected, there are few real consequences for failing to do so. According to WHO's David Heymann, "We have no mechanism for enforcing our recommendations, for example, with respect to destruction of the chimeric viruses. The only way to strengthen this recommendation would be for the World Health Assembly to approve a resolution that the chimeras should be destroyed, but in that case the United States would not sign on. Resolutions are binding on WHO member countries only to the extent that they agree to them."[51] As D. A. Henderson has observed, "If the United States chooses to ignore a recommendation of the WHO Advisory Committee, there are few sanctions that the committee could or would impose."[52]

The effectiveness of the Advisory Committee has been handicapped by a lack of resources. No funding has been made available by member countries to employ a full-time staffer at WHO to support the committee's research. As a result, the WHO Secretariat has not been effective at addressing some of the policy issues concerning smallpox research or engaging the appropriate experts in discussions. Overall, LeDuc observes, "WHO has not taken its oversight role to the next level."[53] The mandate of the WHO Advisory Committee is also limited to technical issues and does not extend to political matters such as destruction of the smallpox virus stocks. Its role is to make recommendations on the steps needed to build an international consensus on when,

[51] Okutani interview with David Heymann, WHO, Geneva, May 7, 2004.
[52] Tucker/Okutani interview with D. A. Henderson, Baltimore, April 27, 2004.
[53] Tucker/Okutani interview with James LeDuc, CDC, September 16, 2004.

from a scientific standpoint, it would be safe to destroy the virus. Any decision on destruction will ultimately be made by politicians, not scientists.

Conclusions

The WHO Advisory Committee on Variola Virus Research has set a useful precedent for the international oversight of scientific work with a lethal and contagious virus. To what extent is this experience applicable to oversight of research with other dangerous pathogens? Is smallpox unique because it involves an eradicated disease for which the causative agent is limited to two official repositories?

According to the CDC's James Hughes, the WHO Advisory Committee "has worked well to bring people together from around the world to evaluate and monitor this activity in a systematic way."[54] By ensuring that smallpox research is subject to international scientific oversight and a high degree of transparency, the process ensures that the live virus used exclusively for benign purposes and has helped to mitigate the fears of other countries that the United States and Russia might exploit their special access to the virus stocks for offensive purposes. At the same time, the value of the review process is limited by the fact that it applies only to "declared" smallpox research. Because the WHO process does not cover any clandestine research on smallpox that may be going on, it may ultimately fail to prevent the illicit use of the virus.

A key element of the institutional design of the WHO oversight system is the separation of political and scientific authority. The 190 WHO member countries represented in the World Health Assembly vote on politically binding resolutions that set the overall direction of the organization's work, but they leave it to scientists to determine how best to achieve the desired results. Although the WHO Advisory Committee must take account of the political environment in which it operates, its oversight of smallpox research is based on scientific peer review, with an emphasis on biosafety and effective experimental design. Another important feature of the Advisory Committee is that the WHO rule requiring broad geographic distribution of its members has increased the international legitimacy of the smallpox research program. Because relevant expertise in poxvirology is not evenly distributed geographically, WHO has also made institutional accommodations, such as the recruitment of non-voting scientific

[54] Tucker/Okutani interview with James Hughes, CDC, July 12, 2004.

advisers, to ensure that peer review of smallpox research is of the highest possible caliber. It will also be critical, however, that any benefits from the research program be widely shared among WHO member states and not subject to exclusive patent rights.

Several aspects of the WHO Advisory Committee process distinguish it from the scientific oversight mechanism currently being developed in the United States. Rather than being limited to scientists, the 25 members of the National Scientific Advisory Board on Biosecurity (NSABB) will represent a variety of different interests—security, intelligence, scientific, and political—complicating the operation of the oversight process. Moreover, in contrast to the WHO Advisory Committee, the NSABB will explicitly consider national security concerns when reviewing scientific research proposals rather than limiting its oversight to scientific and safety issues.

Can international scientific oversight be extended to research with other dangerous pathogens? It is clear that WHO's leadership of the global smallpox eradication campaign enabled it to carve out a central role for itself in determining where and how research with the live smallpox virus is conducted. In view of this precedent, the WHO Advisory Committee process is most directly applicable to polio, which is currently the target of a worldwide vaccination campaign under WHO auspices. If polio eradication is brought to a successful conclusion over the next few years, WHO will probably establish an international advisory committee to examine issues related to the post-eradication research agenda for poliovirus.

Because polio is far less deadly than smallpox and has never been developed as a biological weapon, it does not pose the same magnitude of threat of possible terrorist use. Nevertheless, as soon as poliovirus disappears from nature and the routine vaccination of children ends, serious biosafety and biosecurity concerns will arise, including several issues already encountered with smallpox.[55] For this reason, WHO has begun compiling a comprehensive inventory of laboratories that possess stocks of poliovirus, so that the strain collections can be consolidated and secured. "Locking down" poliovirus will be a daunting task, however, because specimens containing the virus are stored in many thousands of labs around the world and because U.S. scientists recently synthesized poliovirus in the test tube.

[55] D. L. Heymann, et al., "Dangerous Pathogens in the Laboratory: From Smallpox to Today's SARS Setbacks and Tomorrow's Polio-Free World," *Lancet*, vol. 3363 (May 15, 2004), pp. 1566-1567.

To what extent can the WHO Advisory Committee on Variola Virus Research be seen as the embryo of a broader system of international oversight for "contentious" research in the life sciences? Because of the dual threats of emerging infectious diseases and bioterrorism, a growing number of scientists around the world are working with dangerous pathogens, yet no system yet exists for licensing laboratories and researchers involved in such sensitive research. At the same time, new concerns have emerged over the potential malicious use of advances in the life sciences. The Australian mousepox experiment and the synthesis of poliovirus have created the growing conviction, both inside and outside the scientific community, that certain types of potentially hazardous research in the life sciences require international oversight to ensure both safety and security.

In some ways, the current situation resembles that of the early 1970s, when the advent of recombinant DNA technology appeared to pose serious risks for public health and the environment. The Asilomar Conference in February 1975, and the subsequent establishment of the National Institutes of Health guidelines and the Recombinant DNA Advisory Committee, provided an important measure of security and reassurance, while giving scientists rather than politicians primary responsibility for the oversight of their work.[56]

The accelerating pace of research in microbiology and molecular biology is clearly generating risks that warrant a coordinated international response. In October 2004, for example, a research team at the University of Wisconsin published a paper describing the genetic factors that might explain the extraordinarily virulence of the 1918 strain of influenza virus, or Spanish Flu, which killed more than 20 million people worldwide. Using DNA sequences reconstructed from preserved tissues of victims of the 1918 pandemic, the Wisconsin scientists inserted 1918-type DNA segments into ordinary flu virus in order to pinpoint which genes made the virus so lethal. Although this work was initially conducted in a maximum-containment (BSL-4) laboratory in Canada, it was later transferred to a lower-security (BSL-3) laboratory. Publication of the paper sparked a heated controversy over whether or not the research warranted a higher level of

[56] Gregory A. Petsko, "Comment: An Asilomar Moment," *Genome Biology*, vol. 3, no. 10 (September 25, 2002), pp. 1014.1-1014.3 <http://genomebiology.com/content/pdf/gb-2002-3-10-comment1014.pdf>

biocontainment and should have been conducted in the first place. Yet no scientific oversight mechanism was in place to review these decisions in advance.[57]

WHO's central role in the eradication of smallpox and its current effort to eradicate polio give the organization special credibility and authority with respect to the oversight of research involving these two viruses. It seems unlikely, however, that the organization could readily extend its oversight authority to other dangerous pathogens. Although WHO provides important technical advice on the handling of emerging disease agents, such as SARS and monkeypox, it does not exert the same degree of authority over the scope of research being undertaken. Moreover, the causative agents of diseases such as anthrax, plague, and Ebola hemorrhagic fever are all available in nature, and each agent is associated with a unique set of scientific and public health issues that must be addressed individually.

Nevertheless, given the benefits of international scientific oversight of smallpox virus research, including improved accountability, legitimacy, and reassurance about defensive intent, the possibility of creating such a mechanism for all types of "contentious" research in the life sciences should be explored. If and when such a system becomes politically feasible, its basic building blocks are already available in WHO's oversight of smallpox virus research.

[57] Darwyn Kobasa, et al., "Enhanced Virulence of Influenza A Viruses with the Haemagglutinin of the 1918 Pandemic Virus," *Nature*, vol. 431 (October 7, 2004), pp. 703-707'; Nicholas Wade, "Critical Gene a Suspect in Lethal Epidemic," *New York Times*, October 7, 2004, p. A27.

List of published studies and papers
All papers and studies are available as pdf-files at the Commission's website: www.wmdcommission.org

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