Preventing the Misuse of Biology

Lessons from the Oversight of Smallpox Virus Research

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In *The Lessons of History,* published in 1968, Will and Ariel Durant wrote, "One of the discouraging discoveries of our disillusioning century is that science is neutral: it will kill for us as readily as it will heal, and will destroy for us more readily than it can build."[1] Nowhere is this grim truth more evident than in the potential misuse of the life sciences to develop more lethal and effective biological weapons. Studies to investigate the molecular basis of infectious disease and the physiological action of toxins add to the body of scientific knowledge and contribute to the development of new medical therapies. Yet state proliferators or terrorist organizations could apply the same information for hostile purposes, threatening international health and security.[2]

Given the "dual-use" nature of certain types of biomedical investigation, how can society obtain the benefits of this research while minimizing its potential for harm? What is the appropriate balance between limiting biological threats to security and promoting the free and open exchange of ideas that is essential for scientific progress? This article provides an overview of dual-use research in the life sciences, describes some proposals for national and international governance, and examines the case of the World Health Organization's (WHO's) oversight of smallpox research, which provides some useful lessons.

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1. Will and Ariel Durant, *The Lessons of History* (New York: Simon and Schuster, 1968), p. 95.
2. 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/newjournal/articles/tucker.html; Gigi Kwik, Joe Fitzgerald, Thomas V. Inglesby, and Tara O'Toole, "Biosecurity: Responsible Stewardship of Bioscience in an Age of Catastrophic Terrorism," *Biosecurity and Bioterrorism,* Vol. 1, No. 1 (March 2003), pp. 1–9; and Robert Steinbrook, "Biomedical Research and Biosecurity," *New England Journal of Medicine,* November 24, 2005, pp. 2212–2214.

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The Problem of Dual-Use Research

The problem of dual-use research in the life sciences first attracted widespread attention in early 2001, when a team of Australian scientists reported in the *Journal of Virology* that while developing a contraceptive vaccine to control rodent populations, they had inserted the gene for an immune-system protein into the mousepox virus. Unexpectedly, the foreign gene rendered the normally mild virus highly lethal in mice, even those that were naturally resistant to mousepox or had been vaccinated against it.[3] The Australian paper triggered a storm of controversy. Some scientists and security experts criticized the decision to publish the research because it might provide a road map for states or terrorists seeking to develop vaccine-resistant strains of poxviruses that infect humans, such as smallpox or monkeypox.[4]

Several other contentious scientific papers appeared over the next few years. In 2002 Ariella Rosengard and her coworkers at the University of Pennsylvania identified, produced, and characterized a viral protein called SPICE that contributes to the virulence (ability to cause disease and death) of the smallpox virus in humans.[5] That same year, Eckhard Wimmer and his colleagues at the State University of New York at Stony Brook announced that they had constructed infectious poliovirus from scratch by assembling mail-order segments of synthetic DNA, using as a blueprint the published sequence of the viral genome.[6] The synthetic poliovirus contained twenty-seven changes in its DNA sequence to serve as markers, which reduced its virulence a thousandfold. Even so, the experiment demonstrated that creating a dangerous pathogen in the laboratory was no longer in the realm of science fiction. In another controversial study, Nobuyuki Shimono and his colleagues at the University of

3. Ronald J. Jackson, Alistair J. Ramsay, Carina D. Christensen, Sandra Beaton, Diana F. Hall, and Ian A. Ranshaw, "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, No. 3 (February 2001), pp. 1205–1210.

4. Nell Boyce, "Speak No Evil: Should Biologists Publish Work That Could Be Misused?" *U.S. News and World Report,* June 24, 2002, pp. 60–62; and Jon Cohen, "Designer Bugs," *Atlantic Monthly,* Vol. 290 (July/August 2002), pp. 113–124.

5. Ariella M. Rosengard, Yu Liu, Zhiping Nie, and Robert Jimenez, "Variola Virus Immune Evasion Design: Expression of a Highly Efficient Inhibitor of Human Complement," *Proceedings of the National Academy of Sciences,* June 25, 2002, pp. 8808–8813.

6. Jeronimo Cello, Aniko V. Paul, and Eckhard Wimmer, "Chemical Synthesis of Poliovirus cDNA: Generation of Infectious Virus in the Absence of Natural Template," *Science,* August 9, 2002, pp. 1016–1018; and Rick Weiss, "Polio-Causing Virus Created in N.Y. Lab: Made-From-Scratch Pathogen Prompts Concerns About Bioethics, Terrorism," *Washington Post,* July 12, 2002.

California, Berkeley, genetically modified the tuberculosis bacterium to produce a "hypervirulent" strain.[7]

RESURRECTION OF A DEADLY KILLER

Perhaps the most troubling example of dual-use research involved the recreation of the Spanish influenza virus, a formerly extinct pathogen that was responsible for a global pandemic in 1918–19 that killed an estimated 50 million people.[8] In October 2005 Jeffrey Taubenberger and his colleagues at the U.S. Armed Forces Institute of Pathology announced that they had determined the entire DNA sequence of the virus by piecing together fragments extracted from the preserved tissues of 1918 flu victims.[9] Researchers at the U.S. Centers for Disease Control and Prevention (CDC) then used this information to synthesize the Spanish influenza virus in the laboratory, and tested it in tissue culture and mice to identify the genetic factors that made the 1918 strain so deadly.[10] Defenders of this research argued that studying the formerly extinct virus would facilitate the development of vaccines and antiviral drugs against future pandemic strains of influenza. But critics claimed that the research was irresponsible because of the risk that the lethal and contagious virus might escape from the laboratory, and because the decision to resurrect an extinct pathogen had set a dangerous precedent.[11]

Within the next decade, techniques for the automated synthesis of customized DNA strands and their assembly into genes and genomes should make it possible to reconstitute almost any virus whose entire genomic sequence is stored in an online repository, such as the GenBank database maintained by the U.S. National Institutes of Health (NIH).[12] These emerging capabilities

7. Nobuyuki Shimono, Lisa Morici, Nicola Casali, Sally Cantrell, Ben Sidders, Sabine Ehrt, and Lee W. Riley, "Hypervirulent Mutant of *Mycobacterium tuberculosis* Resulting from Disruption of the *mce1* Operon," *Proceedings of the National Academy of Sciences,* December 23, 2003, pp. 15918–15923.

8. John M. Barry, *The Great Influenza: The Epic Story of the Deadliest Plague in History* (New York: Penguin, 2005).

9. Jeffrey K. Taubenberger, Ann H. Reid, Raina M. Lourens, Ruixue Wang, Gouzhong Jin, and Thomas G. Fanning, "Characterization of the 1918 Influenza Virus Polymerase Genes," *Nature,* October 6, 2005, pp. 889–893. See also Jeffrey K. Taubenberger, Ann H. Reid, and Thomas G. Fanning, "Capturing a Killer Virus," *Scientific American,* Vol. 292, No. 1 (January 2005), pp. 62–71.

10. Terence M. Tumpey, Christopher F. Basler, Patricia V. Aguilar, Hui Zeng, Alicia Solórzano, David E. Swayne, Nancy J. Cox, Jacqueline M. Katz, Jeffrey K. Taubenberger, Peter Palese, and Adolfo García-Sastre, "Characterization of the Reconstructed 1918 Spanish Influenza Pandemic Virus," *Science,* October 7, 2005, pp. 77–80.

11. Andreas von Bubnoff, "The 1918 Flu Virus Is Resurrected," *Nature,* October 6, 2005, pp. 794–795.

12. Hamilton O. Smith, Clyde A. Hutchison III, Cynthia Pfannkoch, and J. Craig Venter, "Generating a Synthetic Genome by Whole Genome Assembly: ϕX174 Bacteriophage from Synthetic

have stimulated a debate over whether publishing the DNA sequences of dangerous pathogens, such as the Spanish influenza virus, could generate more risks than benefits. In a 2004 study, the National Research Council, the policy analysis unit of the U.S. National Academies, concluded that the availability of genomic data on microbial pathogens should remain unrestricted because it is critical for the development of new medical therapies.[13]

THE ADVENT OF SYNTHETIC BIOLOGY

In the not-too-distant future, the new techniques of synthetic biology will make it possible to design and build artificial organisms that can perform useful functions, such as manufacturing drugs, destroying cancer cells, and producing hydrogen fuel.[14] Hamilton Smith and his colleagues at the J. Craig Venter Institute in Rockville, Maryland, are redesigning the genome of a tiny bacterium called *Mycoplasma genitalium* by stripping it down to the minimum number of genes needed to support independent life.[15] Eventually, this redesigned bacterium could serve as the basis for creating synthetic microbes with beneficial applications. Despite the promise of synthetic biology, however, the ability to synthesize entire microbial genomes may bring with it new dangers, such as the emergence of a "biohacker" subculture like the one that spawned computer viruses or efforts by states and terrorist groups to exploit the new discipline for hostile ends.[16]

These examples of dual-use research suggest that the accelerating pace of discovery in the life sciences is generating potential threats to international security that warrant a coherent policy response. Given the growing ability to manipulate the most fundamental elements of life, the risk of misuse has become less agent-specific and more inherent in scientific knowledge and know-how. At present, the most likely threat does not come from terrorist organizations, which have limited technical expertise, but from military biologists

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Oligonucleotides," *Proceedings of the National Academy of Sciences,* December 23, 2003, pp. 15440–15445; and Peter Aldous, "The Bioweapon Is in the Post," *New Scientist,* November 9, 2005, p. 8.

13. National Research Council of the National Academies, Committee on Genomics Databases for Bioterrorism Threat Agents, *Seeking Security: Pathogens, Open Access, and Genome Databases* (Washington, D.C.: National Academies Press, 2004).

14. Dan Ferber, "Microbes Made to Order," *Science,* January 9, 2004, pp. 158–161.

15. John I. Glass, Nacyra Assad-Garcia, Nina Alperovich, Shibu Yooseph, Matthew R. Lewis, Mahir Maruf, Clyde A. Hutchinson III, Hamilton O. Smith, and J. Craig Venter, "Essential Genes of a Minimal Bacterium," *Proceedings of the National Academy of Sciences,* January 10, 2006, pp. 425–430.

16. Nicholas Wade, "A DNA Success Raises Bioterror Concern," *New York Times,* January 12, 2005. See also Central Intelligence Agency, Directorate of Intelligence, Office of Transnational Issues, "The Darker Bioweapons Future," OTI SF 2003-108, November 3, 2003.

working in state-level biowarfare programs who keep up with the scientific literature and can funnel basic research findings into weapons development. As advanced biotechnology equipment and know-how spread around the world, however, terrorists may eventually become capable of exploiting these capabilities as well.

Complicating efforts to prevent the misuse of the life sciences is the fact that this field of research is diverse, multidisciplinary, geographically dispersed, and highly dynamic. Moreover, the process of scientific investigation is rarely linear, and unexpected results may surface in midstream. In the case of the Australian mousepox discovery, the dual-use nature of the study did not become apparent until *after* the gene insertion experiment had been carried out. Thus, the "filter" for identifying dangerous research cannot always be applied at the start of a project. Furthermore, the communication of scientific results is not limited to the publication of an article in a peer-reviewed journal but may occur at various times in the course of a study, including conference presentations, preprints, and online postings.

Although restrictions on research are anathema to many life scientists, the failure to provide effective security oversight of potentially dangerous experiments could have serious consequences. If, for example, terrorists were to exploit dual-use information to stage a highly lethal biological attack, public outrage would drive national legislatures to impose draconian controls on scientific inquiry. It is therefore in the enlightened self-interest of the life sciences community to prevent the misuse of their discipline for hostile ends, while striving to make the review and oversight process as reasonable and unburdensome as possible. How can the security risks of dual-use research be managed without causing undue harm to the scientific enterprise?

Proposals for National and International Governance

The dual-use nature of certain types of biomedical investigation raises concerns related both to "biosafety" and "biosecurity." Whereas "biosafety" refers to measures to prevent the accidental infection of laboratory workers and the escape of dangerous pathogens into the environment, "biosecurity" refers to measures to prevent the theft, diversion, and deliberate misuse of disease agents. Biosafety and biosecurity overlap extensively, however, and the distinction is linguistically problematic because many languages do not have separate words for the two concepts.[17]

17. In French, for example, the word *biosecurité* refers both to biosafety and to biosecurity.

The current concerns over dual-use research are reminiscent of those that, in the early 1970s, greeted the advent of recombinant DNA technology (the use of bacterial enzymes to cut and splice genes from different species), which appeared to pose risks for public health and the environment.[18] Seeking to avoid legally binding regulation, U.S. molecular biologists imposed a voluntary moratorium on certain areas of research until the risks were better understood and appropriate safeguards could be developed. In February 1975 the leading investigators in the field met at the Asilomar Conference Center in Pacific Grove, California, to discuss measures to ensure the safety of research involving the creation of recombinant DNA molecules. The Asilomar conference formulated some proposed guidelines, including the obligatory use of weakened strains of bacteria incapable of surviving outside the laboratory to serve as hosts for transferred genes, and the requirement that potentially dangerous experiments be carried out in laboratories equipped with various levels of physical containment, depending on the assessed risk.

The Asilomar recommendations led the U.S. National Institutes of Health to issue the *NIH Guidelines for Research Involving Recombinant DNA Molecules* in 1976.[19] According to these rules, all institutions engaged in NIH-funded research involving recombinant DNA technology must establish institutional biosafety committees (IBCs) to assess the risks of proposed experiments and set requirements for physical and biological containment. Private companies and institutions that do not receive NIH funding are under no obligation to create IBCs, although some have done so voluntarily. Complex issues that cannot be resolved at the IBC level are referred for resolution to a national-level board, the Recombinant DNA Advisory Committee. Over the past three decades, this committee has gradually relaxed the NIH guidelines, which have placed few obstacles in the path of scientific progress.

The relevance of the Asilomar process to the problem of dual-use research goes only so far, for two reasons. First, whereas the 1975 conference focused on the *unintended* risks to public health and the environment that might arise from the accidental release of genetically engineered microorganisms from a research laboratory, today the primary concern is with the *deliberate* misuse of molecular biology to create "designer pathogens" that could injure or kill people, livestock, or crops. Second, a system for the security oversight of dual-use

18. Gregory A. Petsko, "Comment: An Asilomar Moment," *Genome Biology*, September 25, 2002, pp. 1014.1–1014.3, http://genomebiology.com/content/pdf/gb-2002-3-10-comment1014.pdf.
19. National Institutes of Health, *NIH Guidelines for Research Involving Recombinant DNA Molecules* (Bethesda, Md.: National Institutes of Health, rev. April 2002), http://www4.od.nih.gov/oba/rac/guidelines_02/NIH_Gdlnes_lnk_2002z.pdf.

research in the life sciences should ideally go beyond the scope of the NIH guidelines by covering three types of activity: (1) government-funded or privately funded academic studies conducted with the expectation of publication; (2) proprietary research by private industry that is not intended for publication; and (3) classified government research conducted for purposes of threat assessment or biodefense.[20] Each of these categories poses a different set of challenges.

National oversight of dual-use research

In October 2003 an expert committee of the National Research Council, chaired by Gerald Fink of the Massachusetts Institute of Technology, published the report *Biotechnology Research in an Age of Terrorism*.[21] This report warned that the "tools, technology, or knowledge base" of the life sciences could be misused for hostile purposes with potentially catastrophic results, and that "no national or international review body currently has the legal authority or self-governance responsibility to evaluate the proposed research activity prior to its conduct to determine whether the risks associated with the proposed research, and its potential for misuse, outweigh its potential benefits."[22]

The Fink committee identified seven types of "experiments of concern" for which the risks to public health and national security should be evaluated at the funding stage. These potentially dangerous experiments would involve efforts to:

- demonstrate how to render a vaccine ineffective;
- confer resistance to a therapeutically useful antibiotic or antiviral drug;
- enhance the virulence of a pathogen or render a nonpathogen virulent;
- increase the transmissibility of a pathogen;
- alter the range of hosts that a pathogen can infect;
- enable the evasion of diagnostic or detection methods; or
- facilitate the weaponization of a biological agent or toxin.

Experiments on this list could result in findings with a potential for malicious use, such as methods to enhance the virulence, transmissibility, ease of

20. Although classified government biodefense research is probably too sensitive, both technically and politically, to disclose in detail, it should be subjected to careful interagency review to ensure that it complies fully with the legal requirements of the 1972 Biological and Toxin Weapons Convention.
21. National Research Council of the National Academies, Committee on Research Standards and Practices to Prevent the Destructive Application of Biotechnology, *Biotechnology Research in an Age of Terrorism: Confronting the Dual-Use Dilemma* (Washington, D.C.: National Academies Press, 2003).
22. Ibid., p. 107.

dissemination, and environmental stability of dangerous pathogens.[23] It might also be possible to develop disease agents resistant to standard medical countermeasures.[24] To manage these risks, the Fink committee recommended developing a set of criteria for assessing dual-use research and setting up a national mechanism to review proposals and oversee experiments. In addition, in cases where an unexpected scientific discovery posed a threat to public health or national security, the release of the information might have to be restricted, at least temporarily.[25]

In response to the Fink committee report, the administration of President George W. Bush announced in March 2004 the establishment of the National Science Advisory Board for Biosecurity (NSABB) under the auspices of the NIH Office of Biotechnology Activities.[26] This committee, which met for the first time on June 30–July 1, 2005, consists of twenty-five voting members from outside government who have backgrounds in science, security, public health, and intelligence, plus nonvoting ex officio representatives from fifteen federal departments and agencies. The mandate of the NSABB is to recommend strategies for the efficient and effective oversight of dual-use research supported or conducted by the U.S. government.[27] At its first meeting, the advisory board created five working groups devoted to developing (1) an operational definition of dual-use research and a set of guidelines for security reviews, (2) a policy on sensitive scientific communications, (3) a professional code of conduct for the life sciences, (4) a plan for outreach to other countries engaged in dual-use research, and (5) an assessment of the security implications of synthetic genomics.

Defining the criteria for dual-use research is a particularly challenging task. Initially, the NSABB working group limited its focus to "select agents"—the U.S. government's list of pathogens of bioterrorism concern—but later decided

23. Carina Dennis, "The Bugs of War," *Nature,* May 17, 2001, pp. 232–235; Claire M. Fraser and Malcolm R. Dando, "Genomics and Future Biological Weapons: The Need for Preventative Action by the Biomedical Community," *Nature Genetics,* Vol. 29, No. 3 (November 2001), pp. 253–256; and Mark Wheelis, "Biotechnology and Biochemical Weapons," *Nonproliferation Review,* Vol. 9, No. 1 (Spring 2002), pp. 48–53.

24. In 1997, for example, a group of Russian scientists published a paper describing the development of a vaccine-resistant strain of the anthrax bacterium. Although this paper appeared in the open scientific literature, the research had apparently been conducted for the Soviet biological warfare program. See Peter Eisler, "U.S., Russia Tussle Over Deadly Anthrax Samples," *USA Today,* August 19, 2002.

25. National Research Council, *Biotechnology Research in an Age of Terrorism,* pp. 79–106. See also Abigail Salyers, "Science, Censorship, and Public Health," *Science,* April 26, 2002, p. 617.

26. "HHS Will Lead Government-Wide Effort to Enhance Biosecurity in 'Dual Use' Research," *HHS News,* press release, March 4, 2004.

27. NSABB Charter, signed March 4, 2003, http://www.biosecurityboard.gov/charter.asp.

to cast the net more widely to include the synthesis of formerly extinct or eradicated pathogens, as well as experiments that could enhance the ability of a biological agent to inflict harm or increase the susceptibility of the host. This broader definition of dual-use research might also cover "enabling technologies," such as drug delivery systems that generate fine-particle aerosols that can be inhaled into the lungs (the optimal method for delivering biowarfare agents), and "facilitating information," such as societal vulnerabilities that terrorists might exploit.[28] In 2005, for example, two mathematicians at Stanford University developed a theoretical model of how terrorists could contaminate the U.S. milk supply with botulinum toxin. Because this study suggested an effective strategy for carrying out such an attack, the U.S. government requested—unsuccessfully—that it not be published.[29]

Although the founding of the NSABB is an important step forward, the board's power and authority are limited in several respects. First, its recommendations to U.S. government agencies are strictly advisory. Second, important segments of the bioscience research community do not fall under the purview of the board, including the pharmaceutical and biotechnology industries. Third, the NSABB charter specifically excludes the review and oversight of classified biodefense research projects carried out by federal agencies or private contractors, even though such work has dual-use potential.[30]

To conduct security reviews of experiments of concern, the NSABB plans to rely on the institutional biosafety committees that currently oversee recombinant DNA research at NIH-funded universities and research institutes. Only when an IBC cannot reach a decision on a particular research project would the case be referred to the NSABB itself for further adjudication. Critics have challenged the viability of this approach, however, because most IBCs are already overworked and underfunded, and lack the expertise needed to assess the security implications of dual-use research.

The IBC system also appears to be in some disarray. A survey conducted in 2004 by Edward Hammond of the Sunshine Project, a nonprofit advocacy

28. Dennis L. Kasper, "Criteria for Identifying Dual-Use Research and Results," meeting of the National Science Advisory Board for Biosecurity, National Institutes of Health, Bethesda, Maryland, November 21, 2005.
29. Lawrence M. Wein and Yifan Liu, "Analyzing a Bioterror Attack on the Food Supply: The Case of Botulinum Toxin in Milk," *Proceedings of the National Academy of Sciences,* July 12, 2005, pp. 9984–9989.
30. NSABB, "Frequently Asked Questions," http://www.biosecurityboard.gov/faq.asp. For a discussion of the need for oversight of classified biodefense research, see Jonathan B. Tucker, "Biological Threat Assessment: Is the Cure Worse Than the Disease?" *Arms Control Today,* Vol. 34, No. 8 (October 2004), pp. 13–19.

group, found that some institutions conducting NIH-funded research on recombinant DNA do not have a registered IBC, and that many of the existing IBCs do not keep minutes or otherwise fail to conform to the NIH guidelines.[31] Institutions that are noncompliant can theoretically have their NIH research grants revoked; in practice, however, such sanctions have never been imposed. Hammond contends that because of the lack of enforcement, "noncompliance with the guidelines is rampant and the Asilomar commitment has been *de facto* abandoned."[32] In his view, the current system of voluntary self-governance has failed to exercise effective oversight and the only route to full compliance with the biosafety rules would be for Congress to pass legislation creating binding regulations.

INTERNATIONAL OVERSIGHT OF DUAL-USE RESEARCH

Any approach to the oversight of dual-use research in the life sciences must recognize that biotechnology has become a global enterprise with widely dispersed centers of excellence. In addition to the United States, Europe, Israel, and Japan, several developing countries have acquired advanced capabilities in the field, including Brazil, China, Cuba, India, Malaysia, Singapore, South Africa, and South Korea. As the Fink committee report observed, "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."[33] Reports by the Organization for Economic Cooperation and Development and the British Royal Society have also emphasized the need for a harmonized global system to manage the risks of advanced research in the life sciences.[34]

A few nongovernmental analysts have made preliminary proposals for how to organize an international oversight mechanism for dual-use research. In 2001 Gerald Epstein suggested the creation of an international advisory group that would develop uniform guidelines for national regulatory authorities and

31. Sunshine Project, *Mandate for Failure: The State of Institutional Biosafety Committees in an Age of Biological Weapons Research* (Austin: Sunshine Project, October 2004).
32. Edward Hammond, director, Sunshine Project, "Bioscience Oversight," presentation at a seminar sponsored by the Program on Science and Global Security, Princeton University, Princeton, New Jersey, December 2, 2005.
33. National Research Council, *Biotechnology Research in an Age of Terrorism,* p. 12.
34. Organization for Economic Cooperation and Development, International Futures Program, "Promoting Responsible Stewardship in the Biosciences: Avoiding Potential Abuse of Research and Resources," proceedings of a conference held in Frascati, Italy, September 17–19, 2004; and Royal Society, "Do No Harm: Reducing the Potential for the Misuse of Life Science Research," report of a Royal Society–Wellcome Trust meeting, October 7, 2004, http://www.royalsoc.ac.uk/displaypagedoc.asp?id=10309.

the scientific community. He noted, however, that without the negotiation of a treaty through which nations voluntarily accepted the authority of the advisory body, its effectiveness would depend on the extent to which its members were respected by their scientific peers.[35]

More recently, John Steinbruner and his colleagues at the Center for International Security Studies at the University of Maryland (CISSM) proposed a global system for the oversight of dual-use research in the life sciences that would be comprehensive (covering government, academia, and industry), mandatory (with legally binding obligations), and universal (with internationally harmonized procedures and rules). This system would have two key components: a requirement for the licensing of researchers and facilities engaged in dual-use research, including security background checks of scientific personnel; and procedures for the peer review and approval of potentially risky experiments prior to funding, taking into account both the pathogen to be studied and the techniques to be employed.[36]

To carry out the security reviews, the CISSM group envisions a tiered system with three different levels of security review and oversight—local, national, and international—depending on the risks posed by a given experiment. At the first level, local pathogens research committees (similar to IBCs but with legally binding authority) would review *potentially dangerous* experiments that "could significantly increase the destructive potential of agents that would otherwise not be considered a threat." At the second level, a national oversight body would review *moderately dangerous* experiments involving "agents already identified as a threat to public health, particularly activities that enhance the weaponization potential of such agents." Finally, at the third level, a global oversight body, or International Pathogens Research Authority, would review *extremely dangerous* experiments involving "the most dangerous of the current pathogens or that could result in a pathogen significantly more dangerous than currently exists."[37] This third class of experiments would cover geneti-

35. 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 (October–December 2001), pp. 321–354.
36. John Steinbruner, Elisa D. Harris, Nancy Gallagher, and Stacy Okutani, "Controlling Dangerous Pathogens: A Prototype Protective Oversight System," Working Paper (College Park: Center for International Security Studies, University of Maryland, December 2005), pp. 39–41, http://www.cissm .umd.edu/papers/files/pathogens_project_monograph.pdf.
37. John D. Steinbruner and Elisa D. Harris, "Controlling Dangerous Pathogens," *Issues in Science and Technology,* Vol. 19, No. 3 (Spring 2003), pp. 47–54, http://www.issues.org/19.3/steinbruner .htm.

cally modified or synthetic pathogens that combine transmissibility with lethality or some other highly consequential effect.[38] The international oversight body would also determine which research activities are subject to regulation and develop harmonized review criteria for implementation by the participating countries.

A major hurdle to creating such a mechanism is the lack of an existing institutional framework. Whereas the International Atomic Energy Agency plays a leading role in regulating the safety and security of civilian nuclear power plants and radioactive sources, no comparable multilateral organization specializes in biosecurity issues, and the CISSM proposal does not include a political strategy for how such a global research authority could be established, governed, and financed. Indeed, the obstacles facing the creation of such a body appear formidable: the scientific community would be likely to resist legally binding regulations, and national governments would be reluctant to create a new international organization to implement them. Moreover, the national legislative and regulatory frameworks for biosafety and biosecurity vary considerably from one country to another, and there is no international consensus either on which pathogens pose the greatest threat to national security or on the definition of dual-use research.[39] Indeed, much of the developing world views the U.S. preoccupation with bioterrorism to be exaggerated, given the vastly higher death toll inflicted by natural infectious diseases such as AIDS, tuberculosis, and malaria. If history is any guide, countries will be motivated to establish a new global institution only after the accidental or deliberate release of a bioengineered pathogen has caused a major disaster.

To shed some light on more realistic political strategies for the international oversight of dual-use research, it is useful to examine the operation of an existing entity with a limited mandate: monitoring research with the smallpox (variola) virus. Although smallpox was eradicated worldwide in the late 1970s, laboratory studies with the causative virus have continued with the aim of developing medical defenses against its potential use as a military or terrorist weapon. The oversight of smallpox virus research offers some lessons for managing the dual-use dilemma at the international level.

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38. John Steinbruner and Stacy Okutani, "The Protective Oversight of Biotechnology," *Biosecurity and Bioterrorism,* Vol. 2, No. 4 (December 2004), p. 5.
39. For example, the Ebola virus, which is endemic to central Africa, is considered an agent of bioterrorism concern by the United States.

Case Study of Smallpox Virus Research

Headquartered in Geneva, Switzerland, the World Health Organization is a specialized United Nations agency that has 192 member states, or nearly all of the world's countries. WHO investigates disease outbreaks, coordinates public health campaigns, and hosts international forums where technical experts discuss scientific and policy issues and develop action plans. Although WHO suffers from the sluggish bureaucracy typical of large international organizations, it is widely respected for its epidemiological fieldwork, political neutrality, and humanitarian ethos.

Perhaps WHO's greatest accomplishment was the global eradication of smallpox, a contagious disease that killed about a third of its victims and claimed hundreds of millions of lives over the course of human history.[40] Smallpox was finally vanquished in the late 1970s, thanks to a decade-long vaccination campaign coordinated by WHO officials.[41] Even before smallpox had been eliminated, the organization sought to consolidate and secure all known stocks of the virus by urging laboratories around the world to destroy their specimens or transfer them to a designated WHO collaborating center.[42] As a result of this effort, the number of facilities known to possess stocks of the smallpox virus declined from seventy-five in 1975 to only two in 1985—the CDC in Atlanta and the State Research Institute for Viral Preparations in Moscow—which became the sole authorized repositories of the virus.[43]

In 1990 a WHO technical advisory committee called the Ad Hoc Committee on Orthopoxvirus Infections recommended destroying the known stocks of smallpox virus held at the two official repositories by December 31, 1993, after the DNA sequences of representative strains had been analyzed. But delays in the sequencing effort and resistance from scientists interested in studying the

40. 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), pp. 225–230.

41. The smallpox vaccine is a closely related but relatively benign virus called vaccinia, which when inoculated into the skin induces protective immunity against smallpox. For more information on the WHO smallpox eradication campaign, see Jonathan B. Tucker, *Scourge: The Once and Future Threat of Smallpox* (New York: Grove/Atlantic, 2002).

42. World Health Organization, "Smallpox Eradication: Destruction of Variola Virus Stocks," *Weekly Epidemiological Record,* June 18, 1999, p. 188.

43. Frank Fenner, Donald A. Henderson, Isao Arita, Zdeněk Ježek, and Ivan D. Ladnyi, *Smallpox and Its Eradication* (Geneva, Switzerland: World Health Organization, 1988), pp. 1273–1276. See also D.A. Henderson, "Smallpox," in Stacey Knobler, Joshua Lederberg, and Leslie A. Pray, eds., *Considerations for Viral Disease Eradication: Lessons Learned and Future Strategies* (Washington, D.C.: National Academies Press, 2002), pp. 34–40.

molecular biology of the smallpox virus postponed the date of destruction.[44] Meanwhile, in 1994 the Russian government secretly transferred its collection of smallpox virus strains from Moscow to the State Research Center of Virology and Biotechnology, known as "Vector," in Koltsovo, Siberia, informing WHO after the fact.[45] It was not until May 1996 that the World Health Assembly (WHA), the annual meeting of health ministers that is WHO's highest decisionmaking body, adopted a resolution setting a new deadline of June 30, 1999, for destruction of the smallpox virus stocks at the CDC and Vector.[46]

By this time, however, the British and U.S. intelligence services had obtained disturbing information about the Soviet/Russian biological warfare program from two high-placed insiders: Vladimir Pasechnik, who defected to the United Kingdom in 1989, and Kanatjan Alibekov (aka Ken Alibek), who emigrated to the United States in 1992.[47] Both men revealed that in the 1970s, the Soviet military had developed a virulent strain of smallpox virus as a biological weapon and mass-produced it in fertilized chicken eggs at the Soviet Ministry of Defense's Center of Virology in Zagorsk (now Sergiev Posad).[48] Alibekov also disclosed that during the 1980s, the Vector institute had experimented with the use of genetic engineering to develop an "improved" version of the smallpox weapon.[49] Meanwhile, the Central Intelligence Agency obtained circumstantial evidence that undeclared stocks of the smallpox virus might exist in Russia, North Korea, Iraq, and Iran.[50] These suspicions, combined with the progressive decline in the world population's immunity to smallpox, the limited stocks of protective vaccine, and the lack of physician familiarity with the disease, raised fears that the deliberate release of smallpox

44. Lawrence K. Altman, "Smallpox Virus, Frozen in 2 Labs, Escapes a Scalding End for Now," *New York Times,* December 25, 1993.
45. L.S. Sandakhchiev, S.S. Marennikova, and A.A. Guskov, "Status of Variola Virus Stock and Complete Inventory of Isolates at WHO Collaborating Centre, Koltsovo," paper delivered at meeting of WHO Ad Hoc Committee on Orthopoxvirus Infections, Geneva, Switzerland, January 14–15, 1999.
46. World Health Organization, "Destruction of the Smallpox Virus," *Weekly Epidemiological Record,* January 29, 1999, p. 27.
47. Tim Weiner, "Soviet Defector Warns of Biological Weapons," *New York Times,* February 25, 1998.
48. Christopher J. Davis, "Nuclear Blindness: An Overview of the Biological Weapons Programs of the Former Soviet Union and Iraq," *Emerging Infectious Diseases,* Vol. 5, No. 4 (July–August 1999), p. 511.
49. Ken Alibek, with Stephen Handelman, *Biohazard: The Chilling True Story of the Largest Covert Biological Weapons Program in the World—Told from Inside by the Man Who Ran It* (New York: Random House, 1999), pp. 107–122.
50. Barton Gellman, "4 Nations Thought To Possess Smallpox: Iraq, N. Korea Named, Two Officials Say," *Washington Post,* November 5, 2002.

virus by a rogue state or terrorist organization would pose a grave threat to international health and security.

In 1999 the United States decided to seek a delay in the planned destruction of the official stocks of smallpox virus to permit the development of improved defenses against its potential use as a military or terrorist weapon. At the request of the U.S. government, the Institute of Medicine (an arm of the National Academies) developed an agenda for research with the live smallpox virus, including the development of improved diagnostic tools, antiviral drugs, and a safer vaccine.[51] Based on these recommendations, the administration of President Bill Clinton proposed a program of defensive smallpox research under WHO auspices.

On May 22, 1999, the World Health Assembly adopted resolution WHA52.10 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," which would be carried out in a maximum-containment (biosafety level 4) laboratory at each repository. The resolution also stated that all U.S. and Russian research with the live smallpox virus would be financed by voluntary contributions outside the regular WHO budget and would focus on time-limited research objectives necessary to satisfy "outstanding essential needs."[52]

Founding of the WHO oversight committee

To ensure that the smallpox research program was conducted "in an open and transparent manner only with the agreement and under the control of WHO," resolution WHA52.10 mandated the creation of an international group of experts called the Advisory Committee on Variola Virus Research (henceforth Variola Advisory Committee or VAC). This committee would establish "what research, if any, must be carried out in order to reach global consensus on the timing for the destruction of existing variola virus stocks." The VAC would advise WHO on all actions to be taken with respect to the smallpox virus, develop a plan for research with the live virus, review all proposed experiments and oversee their execution, devise a mechanism for reporting the research results to the world health community, and outline an inspection schedule of the

51. Institute of Medicine of the National Academies, *Assessment of Future Scientific Needs for Live Variola Virus* (Washington, D.C.: National Academies Press, 1999).
52. World Health Organization, Fifty-second World Health Assembly, resolution WHA52.10, May 22, 1999. See also Judith Miller and Lawrence K. Altman, "Health Panel Recommends a Reprieve for Smallpox," *New York Times*, May 22, 1999.

two repositories to ensure the strict containment of the existing stocks and a safe and secure environment for work with the live virus.[53] To provide a measure of transparency, minutes of the VAC meetings and abstracts of smallpox research papers would be posted on the WHO website.[54]

To organize the VAC and set up a process for the review of smallpox research proposals, the WHO Secretariat hired Riccardo Wittek, a poxvirologist at the University of Lausanne, Switzerland. Because WHO rules require technical advisory committees to consist of experts from a broad geographical distribution of member states, Wittek recruited eighteen scientists from all six administrative regions of WHO. He also selected several additional experts in virology, public health, and regulation, mostly from Western countries, to serve as nonvoting advisers so the committee would have adequate technical expertise at its disposal. After other countries declined to contribute the roughly $100,000 needed to support the annual operations of the VAC, the U.S. government agreed to cover this expense, as well as fund the smallpox research programs at the CDC and Vector.[55]

The first meeting of the VAC on December 6–9, 1999, began with a lengthy discussion of the merits of retaining the smallpox virus stocks for further study. Several veterans of the smallpox eradication campaign who had witnessed the human devastation caused by the disease—including Isao Arita of Japan, Kalyan Banerjee of India, Frank Fenner of Australia, Peter Greenaway of the United Kingdom, and D.A. Henderson of the United States—called for limiting research with the live virus and setting a date-certain for destruction of the stocks in the two authorized repositories. But other members of the VAC argued that given the Soviet weaponization of the smallpox virus and the risk that undeclared stocks might exist that could fall into the hands of rogue states or terrorists, it was prudent to embark on a broad program of defensive research and development. The two camps finally compromised on a three-year work plan for smallpox research at the CDC and Vector that would end on December 31, 2002.[56]

The VAC identified six research priorities requiring access to the live virus: (1) determining the full or partial DNA sequences of a variety of strains; (2) de-

53. World Health Organization, "Smallpox Eradication: WHO Advisory Committee on Variola Virus Research," *Weekly Epidemiological Record,* February 11, 2000, pp. 45–48.
54. For World Health Organization smallpox research reports, see http://www.who.int/csr/disease/smallpox/research/en/.
55. Riccardo Wittek, interview by author, Geneva, Switzerland, December 4, 2004.
56. World Health Organization, "Future Research on Smallpox Virus Recommended," press release WHO/77, December 10, 1999.

veloping and validating improved diagnostic tests; (3) screening antiviral drugs to identify those most effective for treating smallpox; (4) producing monoclonal antibodies to treat the disease; (5) developing a safer smallpox vaccine; and (6) creating a model of smallpox in macaque monkeys for the efficacy testing of antiviral drugs, vaccines, and diagnostic tests.[57] Some basic research on the genetics and immunology of the smallpox virus would be conducted in parallel with the applied studies, but with specific benchmarks and defined endpoints.[58] The task of reviewing smallpox research proposals prior to their submission to national funding agencies was assigned to the Scientific Subcommittee of the VAC made up of six practicing poxvirologists, including representatives from the CDC and Vector.[59] This group would assess the research proposals for scientific merit, biosafety risks, and consistency with the agreed priorities and timetable.[60]

Several months after the second meeting of the VAC in February 2001, the September 11 terrorist attacks and the subsequent mailing of letters contaminated with anthrax bacterial spores through the U.S. postal system heightened the perceived threat of bioterrorism with the smallpox virus. By the time the VAC met for the third time in early December 2001, it was clear that "significant components" of the smallpox research program would not be completed by the end of 2002, and the committee recommended that the deadline be extended.[61] When the World Health Assembly convened in Geneva in May 2002, it adopted resolution WHA55.15 calling for the "further temporary retention of existing stocks of live virus" for biodefense research, while reaffirming the mandate of the VAC to oversee such work "to ensure that all approved research would remain outcome-oriented and time-limited and periodically reviewed."[62] Unlike previous resolutions, however, WHA55.15 did not set a new

57. World Health Organization, Advisory Committee on Variola Virus Research, "Report of a WHO Meeting," Geneva, Switzerland, December 6–9, 1999, WHO/CDS/CSR/2000.1, pp. 10–15.
58. Donald A. Henderson, "Meeting of the WHO Variola Research Committee," December 6–9, 1999, unofficial memo for the record.
59. In late 2004 the members of the Scientific Subcommittee were Robert Drillien (France), Brian Mahy (CDC), Hermann Schatzmayr (Brazil), Sergei Shchelkunov (Vector), Geoffrey Smith (United Kingdom), and Robert Snoeck (Belgium).
60. World Health Organization, Advisory Committee on Variola Virus Research, "Report of the Second Meeting," Geneva, Switzerland, February 15–16, 2001, WHO/CDS/CSR/EDC/2001.17; and James W. LeDuc, Inger Damon, James M. Meegan, David A. Relman, John Huggins, and Peter B. Jahrling, "Smallpox Research Activities: U.S. Interagency Collaboration, 2001," *Emerging Infectious Diseases*, Vol. 8, No. 7 (July 2002), pp. 743–745.
61. World Health Organization, Advisory Committee on Variola Virus Research, "Report of the Third Meeting," Geneva, Switzerland, December 3–4, 2001, WHO/CDS/CSR/GAR/2002.3, p. 1.
62. World Health Organization, Fifty-fifth World Health Assembly, agenda item 13.16, "Smallpox Eradication: Destruction of *Variola virus* Stocks," WHA55.15, May 18, 2002.

deadline for destruction of the virus stocks at the CDC and Vector. Instead, the duration of the research program was left open-ended pending the completion of the six agreed objectives.

CHANGING DYNAMICS OF THE OVERSIGHT COMMITTEE

Because personal values and assumptions can influence scientific judgments, particularly with respect to uncertain or contentious issues such as global warming and stem-cell research, true impartiality is an elusive goal. For this reason, effective oversight requires a balance among the contending scientific and policy viewpoints within a given field. At the outset, the VAC included several leading experts in epidemiology and public health who believed that the risks of research with the live smallpox virus outweighed the benefits. One of them was Peter Greenaway, the assistant director of research and development at the British Department of Health, who chaired the VAC until 2004. Two other outspoken skeptics on the committee were D.A. Henderson, who had led the WHO smallpox eradication campaign, and Kalyan Banerjee, the former director of the National Institute of Virology in Pune, India. Both argued strongly for limiting research with the smallpox virus and destroying all but a few representative strains.

During the early meetings of the VAC, the skeptics (mostly public health experts) engaged in lengthy debates with the research advocates (mostly virologists), resulting in reasonable compromises that kept the smallpox research program focused on near-term objectives consistent with the 1999 World Health Assembly resolution. As time went on, however, retirements and absences gradually reduced the diversity of opinion on the VAC. By the sixth meeting in November 2004, skeptics such as Henderson and Greenaway had resigned from the committee and been replaced by younger scientists with a professional interest in smallpox research. For example, Greenaway's successor as chairman of the VAC was Geoffrey Smith, a virologist at Imperial College London. Banerjee left the committee under somewhat mysterious circumstances. In 2004 the Indian government notified WHO that he had retired, yet when contacted by the author in October 2004, Banerjee said that he was still interested in serving on the VAC but had not been invited to the next meeting.[63]

Replacing public health experts with virologists shifted the committee's center of gravity in a pro-research direction and weakened the effectiveness of the oversight process. Dissenting opinions became less prominent in the commit-

63. Kalyan Banerjee, email communication to author, October 8, 2004.

tee's deliberations, which began to focus on narrow technical issues rather than the broader safety and security implications of smallpox research. The arcane nature of the discussions also tended to marginalize the remaining public health experts on the VAC, particularly those from developing countries, who contributed little to the debate. According to an observer in late 2004, "The advisory committee still includes several of the best poxvirologists in the world, but most of the people who questioned the value of the research have either left or been diluted out. Those that remain are resigned to the fact that the research program will continue. Thus, opposition is waning even as U.S. pressure to expand the program continues to grow."[64]

CONTENTIOUS ISSUES RELATED TO SMALLPOX RESEARCH

Since its creation in 1999, the VAC has addressed two particularly contentious topics: the fate of hybrid strains of the smallpox virus stored at the CDC, and proposals to authorize the genetic manipulation of the virus. Because of the complexity of these issues, the VAC decisionmaking process is discussed in greater detail below.

PROPOSED DESTRUCTION OF HYBRID VIRUS STRAINS. A persistent source of tension between the VAC and the U.S. government has been the committee's recommendation that a portion of the smallpox virus collection at the CDC be destroyed. During the late 1970s, British virologist Keith Dumbell infected animal cells simultaneously with the smallpox virus and an animal poxvirus (either rabbitpox or cowpox); the two viruses then exchanged genetic material to form hybrids known as "chimeras." Some of these natural recombinants were included in the British smallpox virus collection that was transferred to the CDC in December 1982. Because the British had not inventoried the collection, it was not until 2002 that the CDC learned that the collection contained Dumbell's chimeras. Meanwhile, the development of improved techniques of genetic analysis had eliminated any scientific rationale for studying the hybrid strains.[65]

At the fourth meeting of the VAC in November 2002, the committee recommended unanimously that the chimeric viruses in the CDC collection be destroyed, although their DNA could be copied for archiving.[66] A year later, the

64. Wittek, interview by author.
65. André Plantinga of the Netherlands Vaccine Institute, interview by author, Geneva, Switzerland, November 2, 2004.
66. World Health Organization, Advisory Committee on Variola Virus Research, "Report of the Fourth Meeting," Geneva, Switzerland, November 20–21, 2002, WHO/CDS/CSR/GAR/2003.5, p. 1.

members of the advisory committee (with one dissent) expressed impatience at the CDC's failure to destroy the hybrid strains and urged the WHO Secretariat to "approach the responsible authorities of the collaborating centres to implement the recommendations concerning the destruction of these virus isolates."[67] The U.S. government, however, refused to comply with the VAC recommendation. A spokesperson for the Department of Health and Human Services (HHS), to which the CDC belongs, said that the WHO advisory committee was only "part of the process" of decisionmaking with respect to the smallpox research program and that the United States viewed the hybrid strains as an integral part of the smallpox virus collection that the World Health Assembly had decided to retain for further research.[68]

During the sixth meeting of the VAC on November 4, 2004, the issue of the hybrid strains came up again. CDC virologists argued that the smallpox viral chimeras had potential scientific value and should be retained until the completion of some planned experiments. Because the hybrid viruses were natural recombinants, their responses to antiviral drugs might differ from those of ordinary smallpox virus strains. CDC scientists also wished to determine if smallpox diagnostic tests could recognize the presence of foreign genes in the hybrid viruses. After these experiments had been performed and the viral DNA extracted for archiving, it might be possible to destroy the chimeric strains.[69] CDC officials made clear, however, that any decision on destruction would have to be made at a higher level, presumably by the White House.[70]

The VAC determined that the proposed CDC experiments lacked scientific merit because smallpox viruses that had been engineered deliberately would differ from hybrids created by natural recombination. Accordingly, the advisory committee repeated its recommendation that the chimeric strains be destroyed.[71] The United States, however, continued to defy the VAC. According to a senior White House official, any change in U.S. policy affecting the smallpox virus collection at the CDC would require the approval of all interested federal agencies. The official added that the Bush administration believed that eliminating a portion of the collection would create a troublesome precedent,

67. World Health Organization, Advisory Committee on Variola Virus Research, "Report of the Fifth Meeting," Geneva, Switzerland, November 4–5, 2003, WHO/CDS/CSR/GAR/2004.15, p. 3.
68. Nell Boyce, "Smallpox Mixes Make a Stir," *U.S. News and World Report*, January 19, 2004, p. 64.
69. Joseph J. Esposito, coordinator of collaborative research, CDC, interview by author, Atlanta, Georgia, July 13, 2004.
70. James M. Hughes, director, National Center for Infectious Diseases, CDC, interview by author, Atlanta, Georgia, July 12, 2004.
71. World Health Organization, Advisory Committee on Variola Virus Research, "Report of the Sixth Meeting," Geneva, Switzerland, November 4–5, 2004, WHO/CDS/CSR/ARO/2005.4, p. 3.

leading to international pressure in subsequent years to destroy additional strains. For this reason, the United States planned to resist calls to discard any part of the smallpox virus collection at the CDC until the biodefense research agenda had been completed and access to the live virus was no longer needed.[72]

During the seventh meeting of the VAC on November 10–11, 2005, the committee noted once again that the chimeric viruses still had not been destroyed.[73] CDC scientists reported to the committee that the hybrid strains had been utilized during the previous year "for assessment of new diagnostic strategies" and two had been sequenced, but that no date had been set for their destruction "based on security considerations as determined by United States government officials."[74] Continued U.S. defiance of the VAC has exposed a fundamental weakness in the oversight process, namely WHO's lack of enforcement power. Although the World Health Assembly could theoretically find the United States in violation and suspend its WHO membership, in practice that will never happen—if only because Washington pays a large share of the organization's budget.

REVISION OF THE SMALLPOX RESEARCH GUIDELINES. The other contentious topic addressed by the VAC was the proposed revision of the smallpox research guidelines, which had been drawn up in 1994 by the Ad Hoc Committee on Orthopoxvirus Infections. Among other things, the guidelines prohibited any genetic modification of the smallpox virus. At the third meeting of the VAC in December 2001, U.S. Army virologist John Huggins called for revising the guidelines to permit the insertion into the virus of a "reporter" gene coding for green fluorescent protein (GFP), a jellyfish protein that emits green light when viewed under a fluorescence microscope. The rationale was that use of the GFP gene would make it possible to automate the laboratory screening of antiviral drugs for effectiveness against the smallpox virus. If virus-infected cells glowed green in the presence of a candidate drug, that would signify that the drug had failed to block the replication of the virus and was therefore ineffective; if the cells remained dark, that would indicate that the drug had blocked viral replication and might offer some therapeutic benefit.

72. Kenneth W. Bernard, special assistant to the president for health and biodefense, interview by author, Washington, D.C., May 31, 2004.
73. World Health Organization, Executive Board, 117th sess., "Smallpox Eradication: Destruction of Variola Virus Stocks," Geneva, Switzerland, January 16, 2006, EB117/33, p. 2.
74. World Health Organization, Advisory Committee on Variola Virus Research, "Report of the Seventh Meeting," Geneva, Switzerland, November 10–11, 2005, WHO/CDS/EPR/2006.2, p. 5.

In defense of his proposal, Huggins argued that by limiting the amount of time researchers would need to handle the live smallpox virus, use of the GFP gene would reduce the risk that a researcher might be infected accidentally, the most likely scenario by which smallpox could escape from the laboratory.[75] Nevertheless, although the GFP gene had been introduced into several other viruses without affecting their virulence, some members of the VAC worried that its insertion into the smallpox genome could give rise to unknown hazards. Accordingly, the advisory committee requested "an extensive and reasoned risks analysis" and a consultation with WHO's Biosafety Advisory Group.[76]

In addition to the GFP proposal, the VAC discussed other possible changes to the 1994 research guidelines, such as whether developers of smallpox diagnostic tools outside the CDC and Vector should be given unrestricted access to fragments of the viral DNA up to 500 base-pairs long—too small to code for an entire gene but suitable for use as standards and positive controls.[77] Another proposed change was to permit the insertion into animal poxviruses of individual smallpox viral genes that were potential targets of antiviral drugs. For example, one could insert the smallpox gene coding for DNA polymerase, an enzyme that plays a key role in viral replication, into a related poxvirus. The recombinant virus could then be used to screen antiviral drugs for their ability to inhibit the smallpox viral enzyme without the hazards of working with the live smallpox virus itself.[78] At least potentially, such research might take place outside the two official repositories.

Because of a lack of consensus over the safety implications of the proposed experiments, the VAC created a Technical Subcommittee, made up of six virologists from Britain, Canada, France, Russia, and the United States, to conduct a detailed assessment and prepare recommendations for consideration by the full committee.[79] The composition of this new subcommittee differed from that of the Scientific Subcommittee, although half of the members overlapped.[80]

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75. Deborah MacKenzie, "WHO Allows Genetic Modification of Smallpox Virus," *New Scientist*, November 20, 2004, p. 4.
76. World Health Organization, Advisory Committee on Variola Virus Research, "Report of the Third Meeting," p. 5.
77. World Health Organization, Advisory Committee on Variola Virus Research, "Report of the Fourth Meeting," p. 4.
78. Richard Moyer, University of Florida at Gainesville, telephone interview by author, May 19, 2004.
79. World Health Organization, Advisory Committee on Variola Virus Research, "Report of the Fourth Meeting," p. 3.
80. As of late 2004, the members of the Technical Subcommittee were Inger Damon (United States), Robert Drillien (France), David Evans (Canada), Bernard Moss (United States), Sergei

Due to financial constraints, the Technical Subcommittee deliberated by email rather than in person.[81]

At the VAC's fifth meeting in November 2003, the Technical Subcommittee presented its draft recommendations, which called for revising the 1994 smallpox research guidelines to permit (1) the simultaneous handling of smallpox virus and other poxviruses within the same maximum-containment laboratory; (2) the insertion of the GFP reporter gene into the smallpox virus; (3) the expression of individual smallpox viral genes in related poxviruses; and (4) the unlimited distribution to researchers of fragments of smallpox viral DNA less than 500 base-pairs long.[82] The full VAC accepted the subcommittee's recommendations on the first and fourth issues, but had "significant reservations" about the recommendations on the second and third issues.[83]

In October 2004 Kalyan Banerjee, who had been removed from the VAC at the request of the Indian government, sent an email to the author in which he expressed grave reservations about the draft recommendations:

> It was repeatedly asserted at each meeting of the advisory committee that research with the live virus was permitted only in a time-bound manner, no open-ended research was acceptable, and only the most essential research could be performed. It seems that WHO is out to destroy these principles. If the [GFP] reporter gene is recommended for insertion, what prevents other genes from being inserted? Why not introduce immunosuppressive genes? Who shall provide the guarantee? . . . The expression of variola genes in other poxviruses is a Pandora's box. Do they want to globalize smallpox research? And what is the justification for distributing smallpox gene fragments to all and sundry? If they are to be used as controls for diagnosis, why not define certain DNA segments (no more than two or three) and give them to a few well-recognized laboratories. A free-for-all distribution is absurd.[84]

At the sixth meeting of the VAC in November 2004, the members considered the four recommended changes in the smallpox research guidelines.[85] The discussion focused narrowly on biosafety issues and did not explore whether or not the proposed genetic engineering experiments might open the way to

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Shchelkunov (Russia), and Geoffrey Smith (United Kingdom). Three members of the Technical Subcommittee (Drillien, Shchelkunov, and Smith) also served on the Scientific Subcommittee.

81. Wittek, interview by author.

82. World Health Organization, Advisory Committee on Variola Virus Research, "Report of the Fifth Meeting," pp. 7–8.

83. Ibid., p. 8.

84. Banerjee, email communication to author.

85. World Health Organization, Advisory Committee on Variola Virus Research, "Report of the Sixth Meeting," pp. 6–7.

more dangerous manipulations; the committee simply accepted the view that the research would not set a broader precedent.[86] After deliberations that were characterized as "lengthy but not contentious," the VAC approved all four recommendations, subject to certain conditions.[87] The committee's action was the first step in what WHO officials said would be a "lengthy process" of revising the smallpox research guidelines, including reviews by the director-general, the WHO executive board, and finally the World Health Assembly in May 2005.[88]

Outside observers were harshly critical of the VAC recommendations, arguing that they would lead to a dangerous expansion of research with the live smallpox virus. Former committee member D.A. Henderson opined, "The less we do with the smallpox virus and the less we do in the way of manipulation at this point, I think the better off we are."[89] Sujatha Byravan, executive director of the Council for Responsible Genetics, a nonprofit advocacy group based in Cambridge, Massachusetts, declared, "A decade ago, the WHO was planning to destroy the world's last remaining samples. Today, it is proposing to tinker with the virus in ways that could produce an even more lethal smallpox strain. This is a devastating step backward."[90] In early 2005, two nonprofit ad-

86. Brian Mahy, interview by author, CDC, Atlanta, Georgia, July 12, 2004.

87. The proposed conditions were as follows: insertion of the GFP marker gene into smallpox virus could be performed only in the maximum-containment laboratories at the CDC and Vector; and a "detailed risk analysis" would be conducted for each proposed experiment to ensure that the gene insertion would be "very unlikely" to increase the virulence of the virus. With respect to transfers of smallpox viral genes into related poxviruses, only single genes involved in viral replication (but not virulence) could be transferred, and each proposed experiment would be reviewed in advance by the Scientific Subcommittee, with no guarantee of approval. The gene-transfer experiments would be limited to "enhanced" biosafety level-3 laboratories, or one level of biocontainment higher than was normally required. The VAC also recommended permitting the unlimited distribution of smallpox viral DNA fragments smaller than 500 base-pairs to laboratories and companies developing diagnostic tools, provided that the fragments did not collectively exceed 20 percent of the viral genome. Larger pieces of smallpox viral DNA could be obtained from the CDC or Vector only with the approval of the VAC, and any attempt to assemble the entire virus from fragments of its DNA was "strictly forbidden." World Health Organization, Advisory Committee on Variola Virus Research, "Report of the Sixth Meeting," pp. 10–11. See also Gretchen Vogel, "WHO Gives a Cautious Green Light to Smallpox Experiments," *Science,* November 19, 2004, pp. 1270–1271.

88. Lawrence K. Altman, "WHO Panel Backs Gene Manipulation in Smallpox Virus," *New York Times,* November 12, 2004.

89. Quoted in Steve Connor, "Outcry over Creation of GM Smallpox Virus," *Independent* (London), January 22, 2005.

90. Council for Responsible Genetics, "Plan to Engineer Smallpox Virus Causes Alarm," press release, November 12, 2004, http://www.gene-watch.org/programs/biowarfare/smallpox.html; and Paul Elias, Associated Press, "Smallpox Research Urged by World Health Organization Board," November 12, 2004, *Seattle Times,* November 12, 2004.

vocacy groups, the Sunshine Project and the Third World Network, launched an international public awareness and letter-writing campaign to oppose the VAC recommendations prior to the May 2005 World Health Assembly.[91]

DEBATE IN THE WORLD HEALTH ASSEMBLY

Because of the political sensitivity of the smallpox issue, WHO Director-General Lee Jong-wook personally reviewed the VAC recommendations. In April 2005, a few weeks before the start of the World Health Assembly, he decided to send one of the VAC proposals—for the expression of smallpox viral genes in related poxviruses—back to the advisory committee for further consideration. A memorandum from the director-general's office explained that he "appreciated the need to expedite the development of antiviral drugs and vaccines in ways that do not require the use of live variola virus. Nevertheless, as such research could have broader implications, including certain biosafety and biosecurity concerns, the Director-General recommended that this issue should be reconsidered by the Committee at its next meeting."[92]

Lee allowed the other three VAC recommendations, including the proposed use of the GFP reporter gene, to go to the World Health Assembly for consideration, and WHO officials predicted that member states would adopt the proposals after a "five-minute discussion." In fact, the debate proved to be highly contentious and lasted for a total of two hours on the afternoon of May 19 and the morning of May 20, 2005. Five countries strongly supported the VAC recommendations (Australia, Brazil, Egypt, Russia, and the United States); two were strongly opposed and called for the immediate destruction of the smallpox virus stocks (Iran and Tonga); seven provided conditional support for the proposed experiments but sought to strengthen WHO oversight and set a new deadline for destruction (China, Cuba, Japan, Pakistan, Saudi Arabia, Thailand, and the United Arab Emirates); and three intervened but did not comment on the VAC recommendations (France, Germany, and India).[93]

The views of some countries were more nuanced. The Netherlands opposed proceeding with the GFP experiment because of the potential biosafety risks and urged that all of the VAC recommendations be returned to the committee

91. Sarah Boseley and Julian Borger, "U.S. Scientists Push for Go-Ahead to Genetically Modify Smallpox Virus," *Guardian* (London), May 16, 2005.
92. World Health Organization, Fifty-eighth World Health Assembly, provisional agenda item 13.6, "Smallpox: Destruction of Variola Virus Stocks: Report of the Secretariat," A58/10, April 14, 2005, par. 10.
93. Edward Hammond and Lim Li Ching, "No WHA Endorsement of Genetically Engineered Smallpox Virus: Countries Urge Review of Recommendations and Variola Advisory Committee," Update No. 4, May 21, 2005, http://smallpoxbiosafety.org/who/whareport.html.

for further consideration. Canada and the United Kingdom stressed that any research with the live smallpox virus should be limited to experiments judged essential for public health. South Africa (supported by Zimbabwe) called on WHO to impose a moratorium on research with the live virus until an independent body had been created to examine the VAC recommendations and the oversight process itself. Several delegations urged that the VAC be reformed by preventing smallpox researchers from reviewing their own proposals, ensuring a broader geographical distribution of committee members, and increasing the number of public health and biosafety experts.[94]

Because the World Health Assembly did not take a formal up-or-down vote on the VAC recommendations, it was left to the WHO Secretariat to interpret what the member countries had decided. The assistant director-general for communicable diseases, Anarfi Asamoa-Baah, said that the Secretariat had taken note of the U.S. and Russian interventions in support of the VAC recommendations, as well as the "concerns and cautions" expressed by a large number of member states, and welcomed the suggestion that the VAC should "revisit and review" all of its recommendations. A few days later, however, WHO smallpox program officer Daniel Lavanchy clarified that the VAC would reconsider only one recommendation (on the expression of smallpox genes in related poxviruses), implying that the other contentious proposals had been approved.[95]

THE CHANGING COURSE OF THE COMMITTEE

The criticism of the smallpox research program at the 2005 World Health Assembly appeared to have a significant impact. During the seventh meeting of the VAC on November 10–11, 2005, the committee reviewed the progress of the research and decided that access to the live virus was no longer needed to determine additional DNA sequence information, develop detection and diagnostic tools, or test current and next-generation smallpox vaccines. Moreover, further work with the live virus was warranted in only two areas: (1) obtaining regulatory approval for antiviral drugs by demonstrating their efficacy against the live smallpox virus in test-tube and animal experiments; and (2) continuing to refine the model of smallpox in macaque monkeys so that it more closely resembled the clinical disease in humans.[96] According to CDC scien-

94. Sunshine Project and Third World Network, "No World Health Assembly Approval for Expanding Smallpox Virus Research," news release, May 25, 2005.
95. Martin Enserink, "WHA Gives Yellow Light for Variola Studies," *Science*, May 27, 2005, p. 1235.
96. Because smallpox is a uniquely human disease, inducing the illness in monkeys is difficult and

tists, the goal of the animal research was "to build bridges" between the pathological effects in monkeys of smallpox virus and monkeypox virus, so that the latter model could ultimately be adopted.[97] Still, given the technical challenges involved in developing antiviral drugs and refining the animal model, it could take several more years to complete the smallpox research agenda.[98]

At the request of the WHO director-general, the VAC also reconsidered its recommendation to permit the expression of smallpox viral genes in other poxviruses. According to the meeting minutes, "The Advisory Committee was divided on whether to retain this recommendation. . . . Arguments were made that the use of such recombinants could be justified scientifically . . . [and] that the issues of biosafety could be addressed by including further restrictions on the work. . . . However, the Committee also recognized that the issue was a politically sensitive one and that it could lead to a loss of public confidence in smallpox research. On balance, it was therefore decided that it would be expedient to withdraw the recommendation in its entirety."[99]

Although the VAC did not reconsider its three other recommendations, it did show signs of exerting tighter control over smallpox research. The committee perceived an "urgent" need to review all future research proposals in the light of ongoing progress reports and thereby gain a better perspective on what additional experiments with the live virus were needed. To this end, the VAC asked the United States and Russia to submit written reports on the results of all completed experiments and proposals for future research. The two countries were also asked to resubmit proposals for ongoing research projects because the original proposals had not been reviewed in five years, and "it was considered likely that these would need refinement and re-focus in the light of the progress made."[100] Finally, the VAC tasked the WHO Secretariat to prepare a format for submitting research proposals for review. According to a

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requires intravenous injection of large amounts of the virus; the clinical course of smallpox in monkeys also differs from that in humans.

97. World Health Organization, Advisory Committee on Variola Virus Research, "Report of the Seventh Meeting," p. 9.

98. For descriptions of antiviral and animal model research at the CDC, see Stephen C. Harrison, Bruce Alberts, Ellie Ehrenfeld, Lynn Enquist, Harvey Fineberg, Steven L. McKnight, Bernard Moss, Michael O'Donnell, Hidde Ploegh, Sandra L. Schmid, K. Peter Walter, and Julie Theriot, "Discovery of Antivirals against Smallpox," *Proceedings of the National Academy of Sciences,* August 3, 2004, pp. 11178–11192; and Peter Jahrling, Lisa Hensley, Mark Martinez, James LeDuc, Kathleen Rubins, David Relman, and John Huggins, "Exploring the Potential of Variola Virus Infection of Cynomolgus Macaques as a Model for Human Smallpox," *Proceedings of the National Academy of Sciences,* October 19, 2004, pp. 15196–15200.

99. World Health Organization, Advisory Committee on Variola Virus Research, "Report of the Seventh Meeting," p. 14.

100. Ibid., p. 13.

report on the meeting, "Such a procedure would transparently demonstrate that the Committee was performing its duty to provide oversight of all research involving live variola virus . . . and to ensure that all approved research is outcome-oriented and time-limited."[101]

Ironically, these requests were a tacit admission that since its founding in 1999, the VAC had not fulfilled its mandated functions because it had failed to develop formal procedures for proposal review and research oversight. Early on, the Scientific Subcommittee had approved the broad outlines of the smallpox research program, but from then on it had not reviewed the individual research protocols in detail but had merely been briefed on the results.[102] Although the VAC's belated decision to strengthen its procedures was an important step forward, it remains to be seen how well the new procedures are implemented.

RENEWED DEBATE ON VIRUS DESTRUCTION

In January 2006 the WHO executive board, which sets the agenda for the annual World Health Assembly, discussed the status of the smallpox research program. According to the meeting minutes, "Many speakers confirmed the need to ensure that all approved research remained essential, outcome-oriented, and time-limited. Some board members felt that it was time to consider whether the benefits of destruction of the remaining stocks might not far outweigh those of continued research."[103] This discussion led the executive board to ask the WHO Secretariat to draft a new resolution on smallpox research for consideration by the fifty-ninth World Health Assembly in May 2006. The board also established the Intergovernmental Working Group on Smallpox Eradication, open to all member states, to discuss the draft resolution and make any necessary adjustments.

At a meeting of the intergovernmental working group in Geneva on April 5, 2006, countries from WHO's African Regional Group made a number of suggestions for strengthening the draft resolution. These proposals included setting a new deadline for destruction of the smallpox virus stocks at the CDC and Vector by June 30, 2010; withdrawing authorization to work with the live virus for the purposes of DNA sequencing, diagnostics, and vaccine develop-

101. World Health Organization, Executive Board, 117th sess., "Smallpox Eradication: Destruction of Variola Virus Stocks," p. 3.
102. Third World Network and the Sunshine Project, "Update on Destruction of Variola Virus Stocks," March 2006.
103. World Health Organization, Fifty-ninth World Health Assembly, provisional agenda item 11.5, "Smallpox Eradication: Destruction of Variola Virus Stocks," May 18, 2006, A59/10, p. 4.

ment; and ensuring that all WHO members had access to the benefits of smallpox research, including new antiviral drugs. The African countries also advocated reforming the VAC to include more experts from developing countries and the field of public health. When the United States and Russia rejected the African proposals, the draft resolution was forwarded to the World Health Assembly with large portions of the text set off in square brackets to indicate a lack of consensus support.[104]

On the evening of May 25, 2006, the World Health Assembly debated the draft resolution, and more than two dozen countries made interventions. The Namibian representative, speaking on behalf of the forty-six countries of the African Regional Group, said that the time had come for WHO member states to set a new deadline for destruction of the smallpox virus stocks, ban the genetic engineering of the smallpox virus, and reform the structure and procedures of the VAC. Several states endorsed these proposals, including Cameroon, Iran, Jordan, South Africa, and Thailand. Although the United States opposed setting a new deadline for destruction of the virus stocks, it acknowledged the need to reform the VAC and said it was prepared to negotiate on this topic. Canada, Israel, and the Marshall Islands strongly supported the U.S. position, while Australia and Japan offered more qualified support.[105]

To continue negotiating the draft resolution, the World Health Assembly established a working group, chaired by Thailand, that met twice on May 26 and once more on the morning of May 27, a few hours before the final plenary. In often-heated debate, the U.S. negotiating team (led by William Steiger, director of the HHS Office of Global Health Affairs, and CDC Director Julie Gerberding) refused to consider a new destruction deadline and offered instead to conduct a "major review" of the smallpox research program in 2010. The United States also rejected demands to ban the genetic engineering of the smallpox virus and to withdraw authorization to retain the virus stocks for already completed tasks. It was clear that Washington wished to preserve maximum freedom to continue research with the smallpox virus. Somewhat better progress was made on proposals to reform the membership of the VAC, particularly with respect to geographical origin and area of expertise. But although the African Regional Group argued that it was a conflict of interest for U.S. and Russian smallpox researchers to serve on the VAC and judge the scientific

104. Ibid., pp. 4–7.
105. Edward Hammond, Sunshine Project, "Smallpox Update: WHA Delays Decision on Smallpox Virus Stocks," email listserv, May 30, 2006.

merit and biosafety of their own proposals, the United States refused to exclude CDC and Vector scientists from the committee.[106]

During the final negotiating session, the African countries offered a compromise formula in which they would drop their demand for a new destruction deadline in return for a set of transparency measures, including a major review of all research completed, undertaken, and planned at the two repositories and a detailed report on the research results. But the United States refused to move beyond its proposal to conduct a major review of the research program in 2010.[107] Given the negotiating deadlock, the World Health Assembly referred the draft resolution for consideration by the next session of the WHO executive board in January 2007, and the resolution may well resurface at the May 2007 World Health Assembly.

One reason that it would be wise to set a firm date for destruction of the virus stocks is that within the next decade, advances in synthetic biology could make it possible to synthesize the entire smallpox genome in the laboratory. (Although smallpox viral DNA is not infectious because its replication requires enzymes present in the virus's protein coat, it may be possible to use cells infected with a "helper virus" to get around this problem.) If and when the synthesis of smallpox virus becomes feasible, it will be much harder for the United States and Russia to justify their continued monopoly on research with the live virus. Other countries will insist that if important scientific questions remain to be answered, they should have a right to participate. At a minimum, the moral authority of the United States and Russia to prevent the proliferation of the smallpox virus by banning its synthesis in the laboratory will have been weakened by their persistent refusal to commit to destroying the strain collections under their physical control.

Assessment of the WHO Oversight Process

The history of the VAC provides some useful lessons about the institutional arrangements required for effective international oversight of dual-use research. On the positive side of the ledger, the WHO advisory committee has brought scientists from different countries together to discuss complex technical and policy issues, such as whether or not to permit the genetic engineering of the

106. Ibid.
107. Government of South Africa, "Intervention on Smallpox by the Minister of Health at the Closing Plenary of the 59th World Health Assembly," May 27, 2006.

smallpox virus. According to CDC scientist Joseph Esposito, "I'm impressed by how carefully the issues are vetted—you can sit there for an hour talking over one small point. Most of the time the juice is worth the squeeze."[108]

On the negative side, the VAC has had difficulty exerting effective control over a fast-moving and politically driven research program. According to the Sunshine Project's Hammond, during its first seven years of existence, the advisory committee became "captive to U.S. and, to a lesser extent, to Russian interests."[109] As a result, the VAC was lax in the exercise of its oversight role and sought to expand the smallpox research agenda rather than fulfill its mandate to build consensus on the timing of destruction of the virus stocks. Another major gap in oversight is that the committee did not track the CDC's distribution to outside researchers of short pieces of smallpox DNA, many of which are now unaccounted for. It was only after the VAC came under harsh criticism at the 2005 World Health Assembly that it moved to establish the basic elements of an effective oversight regime, including forms and procedures for reviewing proposals and monitoring research. Given the VAC's mixed record, what lessons can be learned from this experience?

need for balanced membership

The history of the VAC suggests that the international oversight of dual-use research in the life sciences must be insulated from the political pressures imposed by powerful states and other influential stakeholders. Although the members of an oversight committee must have a basic understanding of the relevant scientific issues, it is always possible to commission technical studies by outside experts. More important from the standpoint of effective oversight is for the committee to have a diverse membership that can assess research proposals from a variety of perspectives and takes account of multiple interests, including the public good. One way to preserve this balance over time is to establish fixed quotas of experts from the fields of virology, biosafety, bioethics, and public health. Setting quotas by discipline would also facilitate the task of achieving a broad geographical distribution of experts. Although the developing world has few eminent poxvirologists, it does have many qualified specialists in the fields of public health and epidemiology.

To avoid conflicts of interest, scientists serving on the VAC should not participate in reviewing research projects in which they have a personal, professional, or financial stake. For this reason, smallpox researchers from the CDC

108. Esposito, interview by author.
109. Edward Hammond, interview by author, Geneva, Switzerland, June 11, 2005.

and Vector should not be voting members of the committee but rather nonvoting advisers. In addition, experts should serve on the VAC in a personal capacity and not as government representatives acting under instructions, and, to the extent possible, committee members should be shielded from political or career pressures that might lead them to change their scientific judgments. Finally, VAC members should serve for fixed terms and be removed only in cases of personal wrongdoing or conflict of interest.

NEED FOR GREATER TRANSPARENCY

Another weakness of the VAC has been its lack of adequate measures to ensure transparency and accountability to the World Health Assembly and the public. The committee has generally sought to keep discussions of politically sensitive issues, such as genetic engineering of the smallpox virus, behind closed doors. The annual meetings of the VAC are not announced publicly; the invitation list is limited to voting members, technical advisers, and observers from government agencies; and the meeting minutes are written on a not-for-attribution basis and released after a delay of several months. WHO has also barred representatives from nongovernmental organizations from attending the annual meeting as observers.[110] This lack of transparency has resulted in widespread mistrust of the VAC, which surfaced during the contentious World Health Assembly debates in 2005 and 2006. To restore international confidence in the oversight of smallpox research, it will be necessary to increase the openness of the VAC through more frequent and detailed reporting to WHO member states and by opening up the annual meetings to observers from nongovernmental organizations.

NEED FOR AN IMPROVED FUNDING MECHANISM

The effectiveness of the VAC has also been compromised by the requirement that it must be supported by voluntary contributions outside the regular WHO budget. Because only the United States has been willing to donate money for the operations of the VAC and the smallpox research program, the WHO Secretariat has faced the choice between having an oversight process financed by one country or none at all. Yet the U.S. role as sole funder has given Washington a disproportionate influence over the smallpox research agenda and undermined the objectivity of the oversight process. In addition, funding for the

110. The author's request to attend the November 2004 meeting of the VAC as an observer was initially approved in a letter of invitation from Guénaël R. Rodier of WHO, but the invitation was withdrawn ten days before the meeting, reportedly after the U.S. government objected.

VAC has been too low for the WHO Secretariat to hire a full-time staff member to support the committee or to enable the Scientific Subcommittee to meet in person to review the research protocols.[111]

To correct these problems, WHO should develop an arm's length funding mechanism for the VAC. One approach would be to include the operating costs of the advisory committee as a line item in the regular WHO budget, financed through a small prorated increase in annual dues. Alternatively, wealthy countries other than the United States, such as members of the European Union and Japan, could make voluntary contributions to help cover the cost of VAC operations.

Can the Smallpox Model Be Applied More Broadly?

Assuming that the oversight functions of the VAC become more effective, to what extent could they be applied more broadly to cover other types of dual-use research in the life sciences? Smallpox research is a special case because the virus no longer exists in nature and is held legally at only two repositories. Moreover, the VAC was conceived as a temporary measure until the remaining stocks of the virus have been destroyed.[112]

The smallpox precedent is most directly relevant to polio, which is currently the target of a worldwide eradication campaign coordinated by WHO.[113] Because poliovirus causes serious clinical illness in only about 1 of every 200 infected individuals, it has never been developed as a biological weapon and does not rival smallpox as a security threat. Nevertheless, as soon as the natural transmission of polio has been halted, major biosafety and biosecurity issues will emerge, such as how to destroy or safeguard all laboratory specimens of poliovirus—tens of thousands of which exist worldwide—to prevent an accidental or deliberate release. To address these problems, WHO plans to establish another advisory committee to oversee post-eradication policies for polio.[114]

Although WHO's lead role in the eradication of smallpox and polio gives the organization a strong claim to regulate research involving these two vi-

111. After Riccardo Wittek was hired to staff the VAC in 1999, the University of Lausanne paid his salary for the first year, after which he negotiated a renewable contract with WHO for up to twenty-five days of work annually.
112. World Health Organization, *Life Science Research: Opportunities and Risks for Public Health*, WHO/CDS/CSR/LYO/2005.20 (Geneva, Switzerland: World Health Organization, 2005), p. 15.
113. David Brown, "Global Polio Largely Fading," *Washington Post*, December 26, 2005.
114. David L. Heymann, representative of the director-general for polio eradication, World Health Organization, interview by author, Geneva, Switzerland, November 5, 2004.

ruses, it is far from clear that the WHO could extend its authority to oversee dual-use research more generally. Other dangerous pathogens (such as the causative agents of anthrax, plague, and Ebola hemorrhagic fever) are available from natural sources and cannot be controlled as easily. Still, given WHO's credibility and depth of expertise in the field of newly emerging infections (such as SARS and avian influenza), the organization could plausibly expand its oversight role to regulate research with these agents, as well as with formerly extinct pathogens that have been resurrected in the laboratory (such as the Spanish influenza virus).

An important constraint on WHO's involvement in biosecurity is the need to preserve its political neutrality, which is key to the organization's core public health mission. If WHO were perceived to be meddling in sensitive security matters, certain countries might respond by limiting the organization's access, thus reducing its ability to respond to natural outbreaks anywhere in the world. For this reason, the WHO Secretariat has confined itself to addressing the health and safety aspects of dual-use research. According to WHO official Cathy Roth, "Our role is to ensure that infectious disease research is safe in public health terms for scientific workers and nearby communities."[115] Any effort to expand WHO's role in overseeing dual-use research on newly emerging or synthetic pathogens should therefore be framed in terms of enhancing biosafety and protecting public health rather than preventing deliberate misuse.

Another shortcoming of WHO as a potential regulatory body is that it lacks formal legislative, verification, and enforcement powers. According to David Heymann, a former director of the organization's communicable diseases division, "All WHO can do is review what is going on and convene meetings. The only way to control dangerous technologies on a global basis is through the political pressure of countries on one another. To do that, you have to change the norm of what is acceptable in the international community."[116]

A second possible role for WHO would be to coordinate the development of internationally harmonized criteria for the national oversight of dual-use research in the life sciences. Because expertise in biotechnology is not uniformly distributed worldwide, developing an agreed set of guidelines would require identifying those states with advanced capabilities, seeking out suitable interlocutors, and drawing on the expertise of the Food and Agriculture Organiza-

115. Cathy E. Roth, acting team coordinator, Emerging and Dangerous Pathogens, World Health Organization, interview by author, Geneva, Switzerland, December 2, 2004.
116. Heymann, interview by author.

tion, the World Organization for Animal Health, and scientific societies such as the InterAcademy Panel on International Issues.[117]

Conclusion

WHO oversight of smallpox virus research offers useful lessons for the broader challenge of preventing the misuse of biology at both the national and international levels. The VAC experience suggests that an effective process for the review and oversight of dual-use research in the life sciences requires a mechanism that is insulated from powerful political interests; is funded by diverse countries; incorporates quotas among scientists, biosafety experts, and public health specialists; and provides a large measure of transparency and public accountability. In addition, the oversight process must be based on a common set of guidelines for identifying and assessing dual-use experiments and results that could pose serious risks for international health and security.

117. InterAcademy Panel on International Issues, "IAP Statement on Biosecurity," Trieste, Italy, November 7, 2005.