

- Rao AR. Air sampling to recover variola virus in the environment of a smallpox hospital. *Bull World Health Organ* 1961;25:63-7.
14. Mayhew C, Hahon N. Assessment of aerosol mixtures of different viruses. *Appl Microbiol* 1970;20:313-6.
 15. Thomas DB, Mack TM, Ali A, Muzaffar Khan M. Epidemiology of smallpox in West Pakistan. 3. Outbreak detection and interlocality transmission. *Am J Epidemiol* 1972;95:178-89.
 16. Thomas DB, McCormack WM, Arita I, Khan MM, Islam S, Mack TM. Endemic smallpox in rural East Pakistan. I. Methodology, clinical and epidemiologic characteristics of cases, and intervillage transmission. *Am J Epidemiol* 1971;93:361-72.
 17. Mack T. Smallpox in Europe, 1950-1971. *J Infect Dis* 1972;125:161-9.
 18. Gelfand H, Posch J. The recent outbreak of smallpox in Meschede, West Germany. *Am J Epidemiol* 1971;93:234-7.
 19. Lane J. Smallpox in Yugoslavia: September 22, 1972. CDC Epidemiology Program Report. Atlanta: Center for Disease Control and Prevention, 1972.
 20. Meltzer MI, Damon I, LeDuc JW, Millar JD. Modeling potential responses to smallpox as a bioterrorist weapon. *Emerg Infect Dis* 2001;7:959-69.
 21. Dark Winter: bioterrorism exercise. Washington, D.C.: Andrews Air Force Base, 2001.
 22. Dixon CW. Smallpox. London: J. & A. Churchill, 1962.
 23. Arita I, Shafa E, Kader A. Role of hospital in smallpox outbreak in Kuwait. *Am J Public Health* 1970;60:1960-6.
 24. Palmquist EE. The 1946 smallpox experience in Seattle. *Can J Public Health* 1947;38:213-8.
 25. Weinstein I. An outbreak of smallpox in New York City. *Am J Public Health* 1947;37:1376-84.
 26. Irons JV, Sullivan TD, Cook EBM, Cox GW, Hale RA. Outbreak of smallpox in the lower Rio Grande valley of Texas in 1949. *Am J Public Health* 1953;43:25-9.
 27. Heiner GG, Fatima N, Russell PK, et al. Field trials of methisazone as a prophylactic agent against smallpox. *Am J Epidemiol* 1971;94:435-49.
 28. Kempe CH. Studies on smallpox and complications of smallpox vaccination: E. Mead Johnson Award address. *Pediatrics* 1960;26:176-89.
 29. Marennikova SS. The use of hyperimmune antivaccinia gamma-globulin for the prevention and treatment of smallpox. *Bull World Health Organ* 1962;27:325-30.
 30. Kempe CH, Bowles C, Meiklejohn G, et al. The use of vaccinia hyperimmune gamma-globulin in the prophylaxis of smallpox. *Bull World Health Organ* 1961;25:41-8.
 31. Jackson RJ, Ramsay AJ, Christensen CD, Beaton S, Hall DF, Ramshaw IA. Expression of mouse interleukin-4 by a recombinant ectromelia virus suppresses cytolytic lymphocyte responses and overcomes genetic resistance to mousepox. *J Virol* 2001;75:1205-10.
 32. Neff JM, Lane JM, Fulginiti VA, Henderson DA. Contact vaccinia — transmission of vaccinia from smallpox vaccination. *JAMA* 2002;288:1901-5.
 33. Lane JM, Ruben FL, Abrutyn E, Millar JD. Deaths attributable to smallpox vaccination, 1959 to 1966, and 1968. *JAMA* 1970;212:441-4.
 34. Redfield RR, Wright DC, James WD, Jones TS, Brown C, Burke DS. Disseminated vaccinia in a military recruit with human immunodeficiency virus (HIV) disease. *N Engl J Med* 1987;316:673-6.
 35. 2000 National industry-specific occupational employment and wage estimates: SIC 806 — hospitals. Washington, D.C.: Bureau of Labor Statistics, Department of Labor, 2002. (Also available at http://www.bls.gov/oes/2000/oesi3_806.htm.)

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This article was published at www.nejm.org on December 19, 2002.

Preventing the Return of Smallpox

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Each state party to this Convention undertakes never in any circumstances to develop, produce, stockpile or otherwise acquire or retain: (1) Microbial or other biological agents, or toxins whatever their origin or method of production, of types and in quantities that have no justification for prophylactic, protective or other peaceful purposes; (2) Weapons, equipment or means of delivery designed to use such agents or toxins for hostile purposes or in armed conflict.

— Biological and Toxin Weapons Convention, 1972, Article 1¹

It is imperative and urgent that we prevent the intentional or unintentional release of variola (smallpox) virus into an essentially unprotected global population that continues to benefit from 25 years of freedom from smallpox. During the incubation period of 7 to 17 days, infected persons can travel virtually anywhere in the world before manifesting disease and then spreading it through close respi-

ratory contact with others. In many low-income countries, the disease would be exceedingly difficult to contain. Establishment of smallpox transmission by bioterrorists in one or more countries, particularly low-income countries, would create a global public health emergency. The understandable response to this threat in the United States has been to manufacture and stockpile enough vaccine to cover the entire population, to vaccinate some medical and military staff members and others who will be among the first to respond in the event of bioterrorism, to develop detailed plans for distributing and using the vaccine when it is needed, to confirm the presence of smallpox virus in patients by laboratory testing should there be a bioterrorist event, and to investigate cases and contain the spread of the virus.² Similar preparations are beginning in countries of the European Union and other high-income countries.

The World Health Organization (WHO), concerned especially with helping low-income countries that have a poor health infrastructure, is fo-

ocusing on increasing the global supply of smallpox vaccine and strengthening international capabilities for surveillance, diagnosis, and response.³⁻⁶ In the event of a smallpox outbreak, all countries would investigate and try to contain the outbreak with their own public health and medical services, most of whose personnel are unvaccinated; these public health systems are also facing huge numbers of patients with malaria, human immunodeficiency virus (HIV) infection or AIDS, tuberculosis, and other diseases. The WHO, which also has limited resources with which to battle diseases in low-income countries, would assist countries that were imperiled by smallpox by providing vaccine, personnel, and other resources in the same way that it assists countries in responding to many international outbreaks of disease that are investigated each year.³ Indeed, between January 2000 and March 2002, the WHO investigated 8 reports of suspected smallpox (all of which proved not to be smallpox) and 22 outbreaks of suspected monkeypox (all but 1 of them in the Democratic Republic of Congo) (Heymann D: personal communication). Although the risk of an intentional or unintentional release of smallpox virus remains unquantified and possibly unquantifiable, current plans for a response must be augmented by other actions to prevent the reintroduction of smallpox.

REBUILDING A PLAN

As part of an overall plan to prevent the return of smallpox, we recommend the identification of all persons who have worked in or may have had access to laboratories in which smallpox virus was maintained in recent decades. Assurance that these persons have not illicitly taken isolates out of the laboratory or transferred them to others should be confirmed by direct interviews conducted by special panels set up by national authorities in Russia, the United States, and other countries where smallpox virus is known to exist or to have existed. If any person who has had access to smallpox virus has left the country where the isolates were maintained or is possibly associated with any terrorist group, that information should be shared with the appropriate national and international authorities.

Beginning in 1975, in order to identify all laboratory sources of smallpox virus, the Smallpox Eradication Unit at the WHO contacted all countries and territories requesting a list of laboratories that maintained stocks of the virus, performed a search

of the world's literature, and contacted laboratories directly.^{7,8} All countries should be polled again, since reconfirmation of the absence (or presence) of variola virus in laboratories is warranted; several new nations have gained independence since smallpox was eradicated; laboratory personnel have moved, retired, or died; and security systems at many laboratories have changed, along with other conditions. Special efforts should be directed to countries and groups within countries, particularly military groups, that are known or rumored to have stocks of smallpox virus.⁹

Who should be responsible internationally for such an important and diplomatic mission that can affect the lives of all people? The secretary-general of the United Nations — Kofi Annan, recipient of the 2001 Nobel Peace Prize — should work with heads of state to determine whether smallpox virus exists outside the two WHO collaborating laboratories known to have it, and this information should be shared globally. Why the United Nations instead of the WHO? The secretary-general can communicate directly with heads of state who direct all ministries, including those of defense (where stocks of smallpox virus are alleged to be held in Russia), agriculture, science, technology, education, and health. The United Nations is in contact with all segments of the public and private sectors, including social, political, economic, and military realms, whereas the WHO works primarily with health ministries and related sectors. Moreover, responsibility for management of the Biological Weapons Convention resides with the United Nations.¹⁰

THE NEED FOR SURVEILLANCE

Identification of smallpox dangers today through a strategy of active surveillance, detection, and prevention would be similar in some ways to the policies and actions supported by all countries during the smallpox-eradication campaign. In countries where the disease was endemic, a strategy of door-to-door searches for smallpox by international teams succeeded in eliminating the disease.^{11,12} Every rumor of smallpox was thoroughly and promptly investigated, tens of thousands of specimens were collected, and results were shared widely and promptly.^{7,8} Every country wished to be free of smallpox and not to be menaced by the virus's presence elsewhere or subject to global rebuke for having the disease or retaining stocks of the virus. Reduction of the number of laboratories maintaining stores

of smallpox virus from 76 to 2 took several years of work by the WHO; this work involved many meetings with the directors of laboratories where the virus was kept, on-site inspections, persistent hard bargaining, publicizing of knowledge about which laboratories maintained stores of the virus, and fostering an understanding by all parties of the benefits of eradication.^{7,8}

Currently, the only WHO collaborating centers that maintain smallpox virus are the Centers for Disease Control and Prevention in Atlanta and the State Research Center of Virology and Biotechnology (the Vektor Institute) in Novosibirsk, Russia. Containment in these laboratories must be maintained according to the standards for Biological Safety Level 4 laboratories, and precautions for maximal security are in place. Retention of smallpox virus outside these centers should be declared illegal and criminal. Although laboratory accidents and the unintentional escape of smallpox virus have occurred as recently as 1978, the current strict procedures for containment and periodic inspections should have virtually eliminated this possibility. Yet there are unconfirmed rumors that other countries, and one or more laboratories in Russia in addition to the Vektor Institute, may have smallpox virus.^{9,13,14} The Monterey Institute of International Studies has compiled a list of 12 countries that are known to have biologic-weapons programs, or that probably or possibly have such programs.¹⁵ Apart from the United States and Russia (neither of which is listed as having such a program), no country has been confirmed to have smallpox virus, but the rumors persist.¹⁵

INTERNATIONAL RESPONSIBILITIES

Although the risk of an intentional or unintentional release of smallpox virus is considered to be low, it is real. Hence, our recommendations for preventing such a release are based on the fact that the eradication of smallpox was a global achievement and its maintenance is the responsibility of all countries. Responsibility for the containment of smallpox virus at the national level should rest with heads of state. The secretary-general of the United Nations should be responsible for the containment of the virus at the international level. All countries should now confirm in writing whether or not they have smallpox virus. Countries with smallpox virus should disclose to the secretary-general all places where the virus exists and the security conditions

under which the isolates are maintained; international teams should inspect yearly all places where smallpox virus is kept in order to assure the world that maximal security is maintained. Lists should be compiled of all persons who have had access to smallpox virus in laboratories, as well as of transfers or shipments of smallpox virus from those laboratories, since 1977, the year when the WHO was actively conducting surveys of laboratories and natural transmission of smallpox ended. The current location of each person who has had access to smallpox virus should be determined, and confirmation should be sought that they have not removed the virus from the laboratory, do not currently retain any stores of it, and have not transferred it illegally. If persons who have had access to smallpox virus have moved to another country, that country should be informed, and the persons should be interviewed in their current country of residence.

The illicit retention of smallpox virus and its use should be condemned officially by national and international scientific and medical academies, microbiology societies, and medical organizations. These groups should promote and participate in efforts to reduce the danger of an intentional or unintentional release of smallpox virus. There should be increased support for WHO's programs of epidemiologic surveillance and response, to ensure that all countries, especially low-income countries, can respond effectively to a threatened or actual release of smallpox virus. In addition, all rumors, whatever their source, of potential stores of smallpox virus outside the two WHO collaborating centers known to hold such stores should be investigated immediately by the United Nations; sites with suspected smallpox virus should be inspected immediately, and the results of such inspections should be made public. Finally, the United Nations should hold an international meeting in the near future focused on preventing the use of smallpox virus as a biologic weapon; this meeting should be cosponsored by the two nations that currently retain stocks of smallpox virus.

Retention of smallpox virus outside the two WHO collaborating laboratories should be declared a major criminal offense and should result in condemnation of the country in which the virus is illicitly retained (including censure and sanctions) by member states of the United Nations. The use of the virus as a biologic weapon should be designated a crime against humanity.

THE COSTS AND THE CHALLENGE

The costs of an intentional or accidental release of smallpox virus would be enormous: it would cause anxiety, panic, and disorder globally and would take a high medical and economic toll. An outbreak of smallpox would drain local resources quickly; trigger international quarantine and movement of, and reprisals against, persons, airplanes and other vehicles, and products; limit tourism and investment; and elicit appeals to the WHO, the United States, and other high-income countries for large amounts of vaccine and other resources. (The cost of purchasing vaccine adequate to cover the entire population of the United States is more than \$862 million,¹⁶ about triple what was spent during the 12-year global eradication program.⁸) It is true that the actions we propose would not ensure that all isolates of smallpox virus were identified. Governments, groups, or persons advocating or planning acts of bioterrorism could refuse to respond or could falsify reports. Responses to surveys would not necessarily lead to the validation of information or the performance of inspections. Some governments may not be aware of terrorist groups or persons in their countries who have access to smallpox virus and are planning to release it. However, the implementation of our recommendations would alert all nations to the risks and dangers of a release of smallpox virus and would trigger actions at the national level to protect citizens and others from smallpox.

Hundreds of thousands of health care workers who participated in the smallpox-eradication program have prevented hundreds of millions of persons from acquiring this horrible disease and have prevented tens of millions of deaths. Actions to identify and contain smallpox virus — actions used during the triumph of smallpox eradication — will help maintain the credibility of the organizations responsible for keeping the world free of smallpox. These actions, once again requiring the cooperation of all countries, will increase the confidence of the world's population that governments and international agencies can prevent smallpox from ever appearing again.

The views expressed in this article are those of the authors and do not necessarily reflect those of the institutions with which they are affiliated or the U.S. government.

We are indebted to David Heymann of the World Health Organization and Ciro de Quadros of the Pan American Health Organiza-

tion for information about how their organizations are dealing with a potential bioterrorist release of smallpox.

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1. The Convention on the Prohibition of the Development, Production and Stockpiling of Bacteriological (Biological) and Toxin Weapons and on Their Destruction. Cambridge, Mass.: Harvard Sussex Program on CBW Armament and Arms Limitation, 2001. (Accessed January 10, 2003, at <http://fas-www.harvard.edu/hsp/biologic.html>.)
2. Smallpox response plan and guidelines (version 3.0). Atlanta: Centers for Disease Control and Prevention, November 26, 2002. (Accessed January 10, 2003, at <http://www.bt.cdc.gov/agent/smallpox/response-plan/index.asp>.)
3. Heymann DL, Rodier GR, WHO Operational Support Team to the Global Outbreak Alert and Response Network. Hot spots in a wired world: WHO surveillance of emerging and re-emerging infectious diseases. *Lancet Infect Dis* 2001;1:345-53.
4. Preparedness for the deliberate use of biological agents: a rational approach to the unthinkable. Geneva: World Health Organization, May 2002. (WHO/CDS/CSR/EPH/2002.16.)
5. Global crises — global solutions: managing public health emergencies of international concern through the revised International Health Regulations. Geneva: World Health Organization, 2002. (WHO/CDS/CSR/GAR/2002.4.)
6. Global public health response to natural occurrence, accidental release or deliberate use of biological and chemical agents or radioactive material that affect health. Geneva: World Health Organization, May 18, 2002. (WHA55.16.)
7. Fenner F, Henderson DA, Arita I, Jezek Z, Ladnyi ID. Smallpox and its eradication. Geneva: World Health Organization, 1988. (Accessed January 10, 2003, at <http://www.who.int/emc/diseases/smallpox/Smallpoxeradication.html>.)
8. Breman JG, Arita I. The confirmation and maintenance of smallpox eradication. *N Engl J Med* 1980;303:1263-73.
9. Gellman B. Four nations thought to possess smallpox: Iraq, N. Korea named, two officials say. *Washington Post*. November 4, 2002:A1, A4.
10. Biological Weapons Convention (BWC). New York: United Nations, 2002. (Accessed January 2, 2003, at <http://disarmament.un.org/wmd/bwc/index.html>.)
11. Foege WH, Millar JD, Lane JM. Selective epidemiologic control in smallpox eradication. *Am J Epidemiol* 1971;94:311-5.
12. Basu RN, Jezek Z, Ward NA. The eradication of smallpox from India. New Delhi, India: World Health Organization, South-East Asia Regional Office, 1979.
13. Alibek K. Biohazard: the chilling true story of the largest covert biological weapons program in the world, told from the inside by the man who ran it. New York: Random House, 1999.
14. Preston R. The demon in the freezer: a true story. New York: Random House, 2002.
15. Clinical & biological weapons resource page: chemical and biological weapons: possession and programs past and present. Monterey, Calif.: Monterey Institute of International Studies, 2002. (Accessed January 10, 2003, at <http://cns.miis.edu/research/cbw/possess.htm>.)
16. Connolly C. Smallpox plan may force other health cuts: states cite inability to fund vaccinations. *Washington Post*. December 24, 2002:A1, A5.

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