Sounding Board

Poxvirus Dilemmas — Monkeypox, Smallpox, and Biologic Terrorism

MORE than 20 years have passed since the last case of smallpox was confirmed and 18 years since the International Commission for the Certification of Smallpox Eradication of the World Health Organization (WHO) concluded that the global eradication of smallpox had been achieved.[1,2] Now, new dilemmas confront the world. Could recent outbreaks of human monkeypox in the Democratic Republic of the Congo (known as Zaire from 1971 to 1997)[3-5] represent the return of another form of smallpox?[6] Could variola (smallpox) virus be used as a weapon of biologic terrorism? And what are the implications of the decision of the WHO to advise the destruction of all isolates of the smallpox virus in June 1999?[7]

MONKEYPOX IN HUMANS

Recent reports of large outbreaks of possible cases of monkeypox in the Democratic Republic of the Congo have raised questions as to whether monkeypox could sustain itself as an infection transmitted from human to human, in the same way as smallpox.[3-5] Smallpox vaccine protects against monkeypox, but no one is being immunized against smallpox anymore. Might monkeypox soon take over the ecologic niche left vacant by smallpox?[6] The available data do not support this possibility.

The first case of human monkeypox was identified in 1970, and through 1979, 55 cases of monkeypox were confirmed by the WHO in forested areas of western and central Africa, of which 44 cases (80 percent) occurred in the Democratic Republic of the Congo.[8-10] The clinical picture of monkeypox (Fig. 1) resembles that of smallpox in Central Africa.[9]

The intensified WHO-sponsored field studies between 1980 and 1986 detected an additional 349 cases; virtually all were laboratory-confirmed. The case fatality rate among patients not vaccinated against smallpox was 11 percent (15 percent for children under five years of age).[10] Of patients from the Democratic Republic of the Congo, 72 percent represented primary cases and were presumably infected from an animal source; the others represented spread to a second, third, fourth, and fifth generation of patients.[10,11] Among 431 unvaccinated household contacts, the secondary attack rate was only 9 percent, far lower than the rates of 25 to 40 percent seen with smallpox.[12,13]

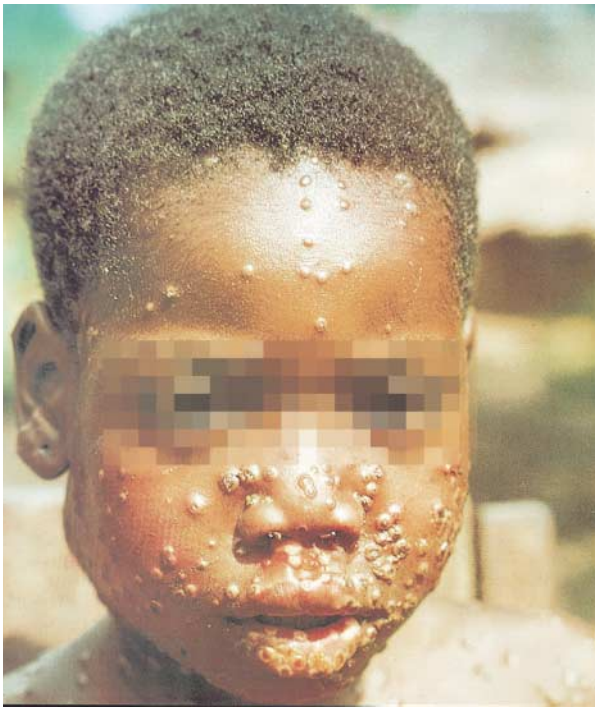
Computer simulations were carried out to determine the likelihood that human-to-human transmission of monkeypox would continue, assuming that vaccination-induced immunity to smallpox fell to zero and secondary attack rates were at the upper 95 percent confidence limits of the observed attack rates — 14 percent for household contacts and 5 percent for nonhousehold contacts.[10,14,15] The model forecast that individual outbreaks might last as long as 14 generations of human-to-human transmission before dying out, but that continuing transmission was highly unlikely.

Only 13 cases of monkeypox were reported from 1987 through 1992, and none from 1993 through 1995.[16] Beginning in February 1996, monkeypox outbreaks in the Democratic Republic of the Congo were reported, but investigations were limited because of civil disorder.[3,4] A joint team from the WHO and the Democratic Republic of the Congo visited the province of Kasai Oriental and concluded that 511 cases of suspected monkeypox had occurred between February 1996 and October 1997.[5,16] Laboratory studies have since revealed that a substantial proportion of the suspected cases were actually cases of varicella; hence, the observed high incidence of possible household transmission (42 percent) was not surprising. Moreover, the disease was relatively mild, and overall case fatality rates were about 1 percent. On the basis of the available data, one cannot conclude that monkeypox has changed genetically or in its pathogenesis, severity, or propensity for human-to-human spread. Careful field studies, to provide more definitive answers, are planned by the WHO.

SMALLPOX AS A BIOLOGIC WEAPON

There is increasing concern that biologic weapons might be deployed in warfare or for terrorist purposes. Terrorism has become more dramatic and destructive in recent years.[17-22] State sponsorship of terrorism has risen, and there is worldwide diffusion of technology both through the Internet and because experts have left laboratories in Eastern Europe. Until recently, smallpox was considered an unlikely agent of bioterrorism because of the high level of population immunity to the disease, the availability of a vaccine, and the knowledge that vaccination of patients' immediate contacts could rapidly control outbreaks.

Circumstances have changed. All vaccination against smallpox ceased after eradication of the disease was affirmed.[1,23] All countries realized substantial savings, both in the costs of vaccine administration and in vaccination-caused illnesses and deaths that were averted.[24] Virtually all children and many adults are now fully susceptible to smallpox. Only limited supplies of vaccine (vaccinia virus) are available. The WHO retains about 500,000 doses of vaccinia, and 60 million to 70 million doses are retained



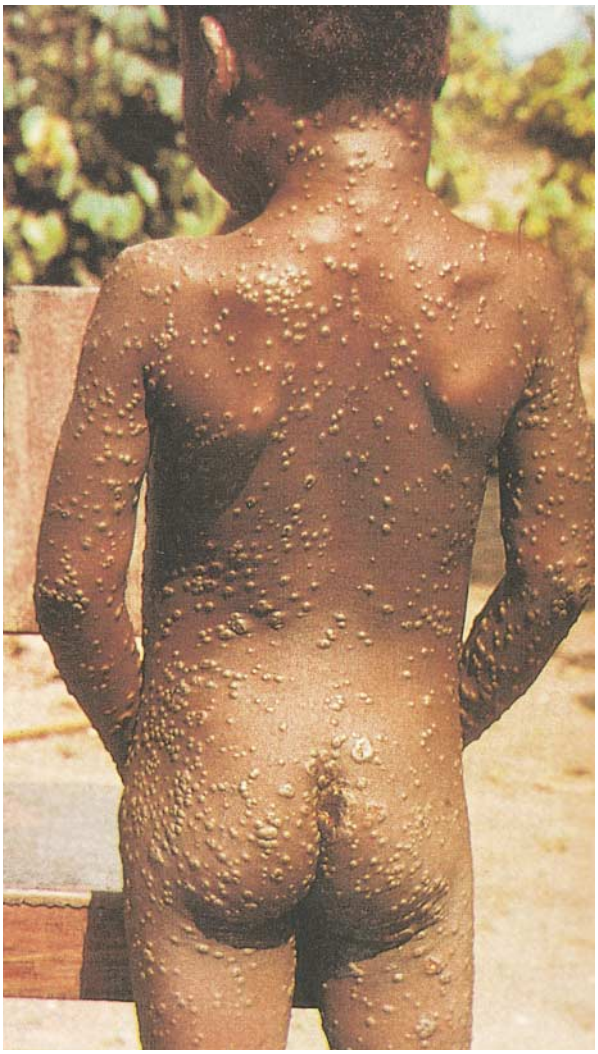


Figure 1. Human Monkeypox in a Six-Year-Old Girl in Zaire, Now the Democratic Republic of the Congo.

In the photographs, taken on about the eighth day of rash, the lesions are all in the same vesiculopustular stage and are concentrated on the extremities, lips, nares, and palms. The child also had cervical and inguinal lymphadenopathy. (Photographs by Mark Szczeniowski.)

elsewhere, not all of which are properly stored or monitored regularly for potency. The U.S. stocks might be adequate to vaccinate 5 million to 10 million persons. Facilities for manufacturing smallpox vaccine have been converted to other uses or destroyed. The production of vaccine in cell culture is under study in the United States, but large-scale manufacture is years away. Genetically engineered vaccinia strains are being investigated, mainly as vectors for other antigens.[25,26]

Where might smallpox virus be obtained? In 1980, the WHO's international commission recommended that "all institutions maintaining stocks of variola virus destroy or transfer these stocks to WHO collaborating centers equipped with adequate security" and that such laboratories be visited at least every two years to evaluate security and adherence to WHO safety directives.[23] Of 76 laboratories identified as having variola virus by 1980, 74 destroyed their stocks or transferred them to a WHO collaborating laboratory.[2] Currently only two laboratories are known to retain variola virus: the Centers for Disease Control and Prevention (CDC) in Atlanta, and the Russian State Research Center of Virology and Biotechnology in Koltsovo, Novosibirsk Region, Russian Federation. Both are WHO collaborating centers and have biosafety-level 4 facilities.

Some speculate that there are additional variola-virus isolates, either long-held unreported stocks or those obtained from a WHO reference center through a lapse in security.[27,28] It has also been hypothesized that smallpox virus has been recombined with other dangerous pathogens for use as a biologic weapon, but the accuracy of these scenarios is unknown.

Were smallpox virus released as an act of terrorism, the results could be catastrophic. A large proportion of the population has no immunity. There is little available vaccine and no effective treatment.

The expected case fatality rate would be higher than 25 percent. Although there are no simple measures to detect or prevent biologic terrorism with smallpox (or other agents),[29] four specific actions could diminish this risk.

First, the WHO should call on all countries to destroy immediately all stocks of variola virus. This would be a clear signal to any group or nation contemplating the use of the virus that such action would be the most reprehensible of crimes.

Second, efforts should be intensified to secure international agreements enforcing inspection of all suspect facilities anywhere in the world. This would include strengthening the Convention on the Prohibition of the Development, Production and Stockpiling of Bacteriological (Biological) and Toxin Weapons and on Their Destruction.[30]

Third, the capacity for large-scale manufacture of additional smallpox vaccine should be developed. Production, with use of WHO-approved vaccinia strains and cell culture, should begin at selected sites and should include the planning of an emergency vaccine-distribution system.

Fourth, a plan to cope with an attack with smallpox virus should be developed as part of a national plan to confront the release of biologic agents. Such an initiative was announced recently by President Bill Clinton.[31] Vaccination should be considered for persons who would be responsible for the investigation and control of suspected outbreaks of smallpox and for patient care.

Although smallpox virus represents an extremely serious threat, the same cannot be said for monkeypox. The effect of an aerosol of monkeypox released among humans is difficult to predict, but case fatality rates would probably be below 15 percent, substantially lower than the rate expected among unvaccinated smallpox victims.[1] Moreover, monkeypox virus is difficult for humans to acquire naturally and has a limited capacity for spread.

DESTRUCTION OF VARIOLA VIRUS

At meetings in 1986 and 1990, a WHO expert committee on orthopoxvirus infections affirmed the desirability of destroying stocks of *Variola major* and *V. minor,* but recommended additional mapping, cloning, and sequencing studies. By 1994, this work was virtually completed, and the committee recommended the destruction of all stocks of variola virus. This decision was supported in 1993 by the Council of the American Society of Microbiology, the executive board of the International Union of Microbiological Societies, the board of scientific counselors of the National Center for Infectious Diseases of the CDC, the board of directors of the American Type Culture Collection, and the Russian Academy of Medical Sciences.

There are cogent arguments for both the destruction and the retention of smallpox virus. Opponents of destruction argue that the unique host specificity of variola virus is justification for its preservation[32-34] and that the virulence segment of the variola-virus genome has not been identified. Studies of variola-virus–encoded proteins that might alter host immune and regulatory functions have been proposed, in the belief that such studies might improve our understanding of human defense mechanisms and help society cope with new poxviruses and other emerging infections.

Proponents of destruction argue that the genomes of reference strains have been cloned and sequenced,[35-37] through cooperative efforts of American and Russian scientists.[38-42] Moreover, monkeypox virus has proved a valuable surrogate for variola: its genomic DNA has more than 90 percent homology with that of variola virus. Monkeypox illness in humans and in macaques closely resembles smallpox in humans, and the disease can be prevented in animals by vaccination. In contrast, there is no satisfactory animal model of smallpox. Work with variola virus must be performed in a biosafety-level 4 laboratory, whereas studies with monkeypox require less stringent precautions. The views of developing countries where smallpox was formerly endemic must also be weighed, since they contributed the most money and human resources to the eradication of smallpox. These countries have advocated the destruction of variola-virus stocks.[7]

During 1995, scientists from the Department of Defense and the Department of Health and Human Services undertook to determine what, if any, studies involving the use of intact variola virus would be critical to public health and national security. It was decided that if a model of monkeypox infection in macaques proved unsatisfactory, studies would be warranted to find a technique to grow variola virus in a genetically or chemically altered mammalian host. The macaque monkeypox model indicated that studies of pathogenesis, the protective efficacy of vaccines, and the therapeutic potential of antiviral compounds could be conducted successfully (Jahrling P, U.S. Army Medical Research Institute for Infectious Diseases: personal communication).

Furthermore, 23 antiviral compounds were evaluated in tissue culture, with comparison of their action against variola, monkeypox, vaccinia, camelpox, and cowpox viruses. Three compounds had significant antiviral activity against variola virus but only moderate inhibitory activity against the other orthopoxviruses. Cidofovir, its cyclic derivative, and ribavirin are in advanced clinical testing or are approved for other viral infections. Further studies of these compounds have begun, with use of a mouse model of cowpox and the macaque monkeypox model (Jahrling P: personal communication). A hypothetical case can be made for the retention of intact variola virus

for as yet incompletely defined research that cannot be conducted with monkeypox virus, cloned variola fragments, or sequence data. This possible use must be balanced against the benefits of a global decision to destroy all stocks of the virus.

CONCLUSIONS

Reports suggesting that monkeypox might replace smallpox as a serious epidemic threat are unsubstantiated, but the threat posed by the possible use of smallpox as a terrorist weapon is genuine. Because of the gravity of this threat, all known stocks of variola virus should be destroyed as soon as possible. The deliberate deployment of this virus must be discouraged by whatever means possible.

JOEL G. BREMAN, M.D., D.T.P.H.
National Institutes of Health
Bethesda, MD 20892-2220

D.A. HENDERSON, M.D., M.P.H.
Johns Hopkins University School of Hygiene and Public Health
Baltimore, MD 21205-2179

The views expressed in this article are those of the authors and do not necessarily reflect the views of the institutions with which they are associated.

We are indebted to Joseph J. Esposito, Karin Esteves, Frank Fenner, David L. Heymann, John W. Huggins, Peter B. Jahrling, Catherine Laughlin, Brian W.J. Mahy, Bernard Moss, and Mark Szczeniowski for their thoughtful comments on the manuscript.

REFERENCES

1. Fenner F, Henderson DA, Arita I, Jezek Z, Ladnyi ID. Smallpox and its eradication. History of international public health. No. 6. Geneva: World Health Organization, 1988.
2. Breman JG, Arita I. The confirmation and maintenance of smallpox eradication. N Engl J Med 1980;303:1263-73.
3. Mukinda VB, Mwema G, Kilundu M, Heymann DL, Khan AS, Esposito JJ. Re-emergence of human monkeypox in Zaire in 1996. Lancet 1997; 349:1449-50.
4. Human monkeypox in Kasai Oriental, Zaire, 1996–1997. MMWR Morb Mortal Wkly Rep 1997;46:304-7. [Erratum, MMWR Morb Mortal Wkly Rep 1997;46:706.]
5. World Health Organization. Human monkeypox in Kasai Oriental, Democratic Republic of the Congo (former Zaire): preliminary report of October 1997 investigation. Wkly Epidemiol Rec 1997;72:369-72.
6. Cohen J. Is an old virus up to new tricks? Science 1997;277:312-3.
7. WHA resolution no. 49.10. Agenda item 18.1. Sixth Plenary Meeting A49/VR/6. Geneva: World Health Organization, 1996.
8. Ladnyi ID, Ziegler P, Kima A. A human infection caused by monkeypox virus in Basankusu Territory, Democratic Republic of the Congo. Bull World Health Organ 1972;46:593-7.
9. Breman JG, Kalisa-Ruti, Steniowski MV, Zanotto E, Gromyko AI, Arita I. Human monkeypox, 1970–79. Bull World Health Organ 1980;58:165-82.
10. Jezek Z, Fenner F. Human monkeypox. Vol. 17 of Monographs in virology. Basel, Switzerland: Karger, 1988.
11. Jezek Z, Grab B, Szczeniowski MV, Paluku KM, Mutombo M. Human monkeypox: secondary attack rates. Bull World Health Organ 1988; 66:465-70.
12. Rao AR, Jacob ES, Kamalakshi S, Appaswamy S, Bradbury BD. Epidemiological studies in smallpox: a study of intrafamilial transmission in a series of 254 infected families. Indian J Med Res 1968;56:1826-54.
13. Foster SO, Smith EA. The epidemiology of smallpox in Nigeria. J Nigeria Med Assoc 1970;7:41-5.
14. Fine PE, Jezek Z, Grab B, Dixon H. The transmission potential of monkeypox virus in human populations. Int J Epidemiol 1988;17:643-50.
15. Jezek Z, Grab B, Dixon H. Stochastic model for interhuman spread of monkeypox. Am J Epidemiol 1987;126:1082-92.
16. Heymann DL, Szczeniowski M, Esteves K. The resurgence of monkeypox in Africa. Br Med Bull 1998;54:691-700.
17. Kupperman RH, Smith DM. Coping with biological terrorism. In Roberts B, ed. Biological weapons: weapons of the future. Washington, D.C.: Center for Strategic and International Studies, 1993:35-46.
18. Betts RK. The new threat of mass destruction. Foreign Aff 1998;177: 26-41.
19. Simon JD. Biological terrorism: preparing to meet the threat. JAMA 1997;278:428-30.
20. Henderson DA. Bioterrorism as a public health threat. Emerg Infect Dis (in press).
21. Zilinskas RA. Iraq's biological weapons: the past as future? JAMA 1997;278:418-24.
22. Simon JD. Terrorists and the potential use of biological weapons: a discussion of possibilities. Santa Monica, Calif.: RAND Corporation, 1989.
23. The global eradication of smallpox: final report of the Global Commission for the Certification of Smallpox Eradication, Geneva, December 1979. History of international public health. No. 4. Geneva: World Health Organization, 1980.
24. Lane JM, Ruben FL, Neff JM, Millar JD. Complications of smallpox vaccination, 1968: national surveillance in the United States. N Engl J Med 1969;281:1201-8.
25. Sutter G, Moss B. Novel vaccinia vector derived from the host range restricted and highly attenuated MVA strain of vaccinia virus. Dev Biol Stand 1995;84:195-200.
26. Moss B. Genetically engineered poxviruses for recombinant gene expression, vaccination, and safety. Proc Natl Acad Sci U S A 1996;93:11341-8.
27. Garrett L. Inside a biowar lab. Newsday. August 10, 1997:1.
28. Preston R. Annals of warfare: the bioweaponeers. New Yorker. March 9, 1998:52-65.
29. Franz DR, Jahrling PB, Friedlander AM, et al. Clinical recognition and management of patients exposed to biological warfare agents. JAMA 1997;278:399-411.
30. Kadlec RP, Zelicoff AP, Vrtis AM. Biological weapons control: prospects and implications for the future. JAMA 1997;278:351-6.
31. Remarks by the President at the United States Naval Academy commencement, May 22, 1998. White House press release, Washington, D.C., May 22, 1998.
32. Joklik WK, Moss B, Fields BN, Bishop DH, Sandakhchiev LS. Why the smallpox virus stocks should not be destroyed. Science 1993;262: 1225-6.
33. Roizman B, Joklik W, Fields B, Moss B. The destruction of smallpox virus stocks in national repositories: a grave mistake and a bad precedent. Infect Agents Dis 1994;3:215-7.
34. Joklik W. The remaining smallpox virus stocks are too valuable to be destroyed. Scientist 1996;10:11.
35. Mahy BWJ, Esposito JJ, Venter JC. Sequencing the smallpox virus genome: prelude to destruction of a virus species. ASM News 1991;57:577-80.
36. Mahy BW, Almond JW, Berns KI, et al. The remaining stocks of smallpox virus should be destroyed. Science 1993;262:1223-4.
37. Mahy BWJ. The WHO recommendations to destroy all smallpox stocks should be enacted without delay. Rev Med Virol 1993;3:131-2.
38. Massung RF, Liu L, Qi J, et al. Analysis of the complete genome of smallpox variola major virus strain, Bangladesh-1975. Virology 1994;201: 215-40.
39. Massung RF, Loparev VN, Knight JC, et al. Terminal region sequence variations in variola virus DNA. Virology 1996;221:291-300.
40. Senkevich TG, Bugert JJ, Sisler JR, Koonin EV, Darai G, Moss B. Genome sequence of a human tumorigenic poxvirus: prediction of specific host response-evasion genes. Science 1996;273:813-6.
41. Massung RF, Esposito JJ, Liu LI, et al. Potential virulence determinants in terminal regions of variola smallpox virus genome. Nature 1993; 366:748-51.
42. Shchelkunov SN, Massung RF, Esposito JJ. Comparison of the genome DNA sequences of Bangladesh-1975 and India-1967 variola viruses. Virus Res 1995;36:107-18.