Smallpox and American Indians Revisited

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Abstract. Smallpox ravaged the people of Europe and the Americas in the early modern era. Why it was a catastrophic cause of death for American Indians that helped lead to severe depopulation, but a manageable cause among Europeans that allowed continued population growth, has puzzled scholars. Research on variola continued after smallpox eradication in 1977, prompted in part by the fear that aerosolized smallpox might be used in bioterrorism. That research updates factors that may have aggravated smallpox lethality in American Indians, giving new information about infectivity, the proportion of people who may have contracted smallpox, the burden on infants of mothers who had not had smallpox, and the toll for pregnant women. This essay reviews old and new hypotheses about why so many in the New World died from smallpox using recent smallpox research and older sources. ***Keywords:*** smallpox, American Indians, variola major, variola minor, maternal antibody, smallpox transmission, hypotheses about lethality.

Europeans who saw smallpox in epidemics among New World Indians were shocked by how much more lethal this disease was in the Americas than what they had known at home. That was true in the sixteenth century, when the comparison was usually between a severe disease in the New World and a mild counterpart in Europe. It remained true in the period 1650–1800, when lethal variants of smallpox dominated in both regions. Even though smallpox was the leading cause of death in eighteenth-century Europe, accounting for between 5 and 10 percent of all

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deaths, it was more devastating still in the New World. In Europe, smallpox slowed population growth. In the Americas, it was the chief factor in the depopulation of the American Indians.

Witnesses of smallpox in the Americas tried to understand why larger proportions of people seemed to die in New World outbreaks. Historians have continued this, searching for explanations and offering hypotheses. The aim in this essay is to test current hypotheses using evidence acquired in recent smallpox studies, and to consider new ideas about why this disease was deadlier in America than in Europe.

SMALLPOX IN EUROPE AND THE NEW WORLD, 1500–1900

Unfamiliar diseases arrived in the New World with the Europeans and their African slaves, causing sometimes heavy, even catastrophic, mortality in initial outbreaks as well as in accumulation. Highly lethal epidemics persisted into the nineteenth century in more remote settlements newly exposed or re-exposed to Old World diseases. However, smallpox seems never to have established an endemic presence in more remote areas, and may not have done so anywhere in the Americas before the 1790s when it is reported to have become endemic in Mexico.[1] Up to that point, and perhaps afterwards as well, smallpox was re-introduced time and again from Africa and Europe, sometimes via the West Indies, and from other parts of the Americas.

At the beginning of the sixteenth century, smallpox was endemic in Europe and the principal variant in circulation appears to have been mildly lethal, either variola minor or a similar type. By the latter part of that century, both high and low-lethality variants were reported.[2] In Britain, highly lethal smallpox came to dominate

1. S. F. Cook, "The Smallpox Epidemic of 1797 in Mexico," *Bull. Hist. Med.*, 1939, *7*, 937–69. Consecutive epidemics over two or more decades, spaced a few years apart, signal endemic smallpox, even if temporary. So do reports that smallpox was mainly a disease of childhood.

2. For reports of lethal smallpox, see Carlo Marco Belfanti, "Una città e la carestia: Mantova, 1590–1592," *Ann. Foundazione Luigi Einaudi*, 1982, *16*, 99–140; Alfred Perrenoud, "La mortalité à Genève de 1625 à 1825," *Ann. Démog. Hist.*, 1978, 209–33; and Robert McCaa, "Spanish and Nahuatl Views on Smallpox and Demographic Catastrophe in Mexico," *J. Interdis. Hist.*, 1995, *25*, 397–431, 418. For reports of mild smallpox, see Ann G. Carmichael and Arthur M. Silverstein, "Smallpox in Europe before the Seventeenth Century: Virulent Killer or Benign Disease?" *J. Hist. Med. Allied Sci.*, 1987, *42*, 147–68; McCaa, "Spanish and Nahuatl Views," 418–19; and Charles Creighton,

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toward the middle of the seventeenth century, establishing itself there and on the Continent as the leading cause of death and retaining that position up to the introduction of vaccination in 1798.[3] Less detail is available about Asia in the same period, but there the smallpox that was discussed in medical texts and other sources was a lethal variant.[4]

In Africa, the earliest reports that characterize smallpox lethality describe it as mildly lethal in some outbreaks and severely lethal in others. People taken as slaves in the interior proved susceptible to smallpox, which circulated on the coast. Slavers tried to avoid taking on board anyone with an active case, but could not distinguish people already infected but still incubating this disease. Thus after departure slaves on board were often sick with smallpox; sometimes many died, and sometimes only a few. On the coast, too, smallpox reappeared periodically, such as at the Dutch fort at Elmina, on the Guinea coast, every thirteen or fourteen years. In some epidemics it killed thousands, while in others it was less dangerous for Africans than for Europeans.[5]

Outbreaks of smallpox in the New World in the sixteenth century certainly included at least one severely fatal variant. Lethal smallpox circulated in Mexico in 1520, and then moved into

A History of Epidemics in Britain, 2 vols. (Cambridge: Cambridge University Press, 1891–1894), II: 436, 441. Smallpox appears in several variants, sometimes called strains or clades, which vary in lethality with variola major occupying a distinctive place in the top rank and other variants showing lower age-specific case fatality rates that overlap in at least one age group. Sources cited in n. 10 seek the genetic bases of these variations.

3. Peter Sköld, *The Two Faces of Smallpox: A Disease and Its Prevention in Eighteenth- and Nineteenth-Century Sweden* (Umeå: Demographic Data Base, Umeå University, 1996); Pierre Darmon, *La longue traque de la variole: Les pionniers de la médicine préventive* (Paris: Libr. académique Perrin, 1986); Creighton, *History of Epidemics in Britain*; and J. R. Smith. *The Speckled Monster: Smallpox in England, 1670–1970, with Particular Reference to Essex* (Chelmsford: Essex Record Office, 1987).

4. Chia-Feng Chang, "Aspects of Smallpox and Its Significance in Chinese History" (PhD diss., University of London, 1996), 124–68 and passim; Ann Bowman Jannetta, *Epidemics and Mortality in Early Modern Japan* (Princeton: Princeton University Press, 1987), 68, 78–86, and passim; and Ralph W. Nicholas, "The Goddess Sitala and Epidemic Smallpox in Bengal," *J. Asian Stud.*, 1981, *41*, 21–44.

5. Thomas Phillips, "A Journal of a Voyage from England to Africa, and so Forward to Barbadoes, in the Years 1693 and 1694," in *A Collection of Voyages and Travels*, ed. John Churchill, 6 vols. (London, 1732), VI: 173–239; and William Bosman, *A New and Accurate Description of the Coast of Guinea, Divided into the Gold, the Slave, and the Ivory Coasts*, 2nd ed., trans. from Dutch (London, 1721), 37–38 and 94, among other sources, give firsthand accounts of smallpox on the African coast and on shipboard.

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Central America. Similar outbreaks began in Brazil in 1562, each time on the coast, and each time in association with the arrival of vessels from Europe or Africa. The 1562–65 epidemic came from Portugal, while the epidemics of 1597, the 1680s, and repeatedly during the eighteenth century came from West Africa. The 1613 outbreak originated in Central Africa and the Lower Guinea coast of today's Togo, Benin, and southwestern Nigeria, and outbreaks of the 1620s, 1660s, and 1710s in Angola. By the end of the eighteenth century, smallpox was arriving from Mozambique as well.[6] African slaves were so susceptible to smallpox, on the African coast, on shipboard, and in the New World, that a constant flow of new slaves was required to make up for losses due to smallpox among earlier arrivals.[7]

References to mildly lethal smallpox outbreaks in the New World appear in 1530–31, 1538, and 1615–16. They may describe variola minor or another mild variant, or they may confuse smallpox with measles.[8] The earliest known medical description of the variola minor variant that came to be called alastrim dates from 1863 in Jamaica.[9]

These references, and the chronologies posited by genome sequencing teams,[10] indicate that both lethal and mild smallpox

6. Dauril Alden and Joseph C. Miller, "Out of Africa: The Slave Trade and the Transmission of Smallpox to Brazil, 1560–1831," *J. Interdis. Hist.*, 1987, *18*, 196–224, esp. 199–208; and Dauril Alden and Joseph C. Miller, "Unwanted Cargoes: The Origins and Dissemination of Smallpox via the Slave Trade from Africa to Brazil, c. 1560 to 1830," in *The African Exchange*: *Toward a Biological History of Black People*, ed. Kenneth F. Kiple (Durham, North Carolina: Duke University Press, 1987), 35–109. Brazilian authorities tried to prevent the importation of smallpox by quarantining ships, but rarely with much effect.

7. Alden and Miller, "Unwanted Cargoes," 41.

8. The epidemic of 1531–1532 in Mexico was identified as smallpox by some observers and measles by others, and thus may represent a variola minor outbreak. Robert McCaa, "Revisioning Smallpox in Mexico City-Tenochtitlán, 1520–1950: What Difference Did Charity, Quarantine, Inoculation and Vaccination Make?" in *Living in the City: 14th–20th Centuries: Proceedings of the International Conference Held by [the] International Commission for Historical Demography, Rome, September 27–29, 1999*, ed. E. Sonnino (Rome: Casa Editrice Università La Sapienza, 2004), 455–88.

9. Izett Anderson, "On Epidemic Varioloid Varicella in Jamaica," *Trans. Epidemiol. Soc. Lond.*, 1866, *2*, 414–18. Anderson distinguishes smallpox in this outbreak, which occurred in 1863, from "genuine variola," varioloid (a mild infection usually associated with vaccination), and chickenpox, but does not name it. Anderson allowed his patients, inmates of a penitentiary and some seen in private practice, to follow their regular routine because their cases were so mild.

10. J. J. Esposito et al., "Genome Sequence Diversity and Clues to the Evolution of Variola (Smallpox) Virus," *Science*, 2006, *313*, 807–12; Yu Li et al., "On the Origin of

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variants were in circulation in Europe and Africa in the sixteenth century. The New World repeatedly imported lethal smallpox from both Africa and Europe, and may also have repeatedly imported one or more mild variants. Variola major may have emerged first in Asia; it appeared in China in the fourth century and had a continuous existence there from the tenth century AD into the 1960s. Mild variants may have emerged first in Africa; by the 1960s, separate mild variants of variola minor circulated in different parts of Africa, along with variola major variants that may have been milder than what was familiar in Europe or Asia.[11]

Infection with any orthopoxvirus protects against subsequent infection with any other. Thus had variola minor or any mild variant circulated widely in the New World, the population would have been protected against variola major. Since most epidemics for which an indication is available killed large numbers of people, mild variants did not circulate widely. Nor were American Indians exposed to other orthopoxviruses. Two occur in the Americas, but humans are not known to be susceptible to either.[12] The migration of American Indians from Asia was probably completed before variola appeared in Asia.[13] Thus the indigenous population of the Americas was susceptible to smallpox, not because of any immune system deficit but because those people had not previously been exposed. The smallpox they suffered was mainly a lethal variant, presumably variola major, which reappeared periodically in the Americas in devastating epidemics.

A disease that may have been smallpox reached the West Indies during the 1490s. Smallpox appeared in Hispaniola in 1518, killing

Smallpox: Correlating Variola Phylogenics with Historical Smallpox Records," *Proc. Natl Acad. Sci. USA*, 2007, *104*, at www.pnas.org/content/104/40/15787 (accessed 4 February 2010); and I. V. Babkin and S. N. Shchelkunov, "Molecular Evolution of Poxviruses," *Rus. J. Genet.*, 2008, *44*, 1029–44.

11. On smallpox in Asia see n. 4. On smallpox in modern Africa, see Esposito et al., "Genome Sequence Diversity."

12. Those are raccoonpox and volepox. Bernard Moss, "Poxviridae: The Viruses and Their Replication," in *Fields' Virology*, 5th ed., ed. David M. Knipe and Peter M. Howley, 2 vols. (Philadelphia: Lippincott, Williams, and Wilkins, 2007), II: 2905–45, 2906.

13. The most recent migrations from Asia are dated to c. 12,000 BP, well before the period in which Li et al. estimate the divergence of variola minor from ancestral variola. M. H. Crawford, *The Origins of Native Americans: Evidence from Anthropological Genetics* (Cambridge: Cambridge Univ. Press, 1998), 16, 19, and 25.

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between one-third and one-half of the Indians, but few Spaniards. An outbreak began in Mexico in April 1520, and spread slowly inland, moving from place to place at the deliberate pace associated with this disease and its pre-infective period of more than two weeks (i.e., the incubation period plus additional days to the point of infectiveness). In five months, from May to September, the epidemic moved across some 150 miles, easing the Spanish conquest of Mexico, and was finally exhausted in January 1521. Again the Spanish seem not to have been susceptible. That was the first of a number of epidemics, which did not subside until about 1900, and which appeared and re-appeared in Native American communities throughout the Americas, including the Caribbean, and in Greenland.[14]

14. McCaa, "Spanish and Nahuatl Views"; McCaa, "Revisioning Smallpox"; Robert McCaa, "The Nahua *Calli* of Ancient Mexico: Household, Family, and Gender," *Contin. Change*, 2003, *18*, 23–48; Alden and Miller, "Unwanted Cargoes"; Alden and Miller, "Out of Africa"; Henry F. Dobyns, "An Outline of Andean Epidemic History to 1720," *Bull. Hist. Med.*, 1963, *37*, 493–515; Henry F. Dobyns, "Disease Transfer at Contact," *Annu. Rev. Anthropol.*, 1993, *22*, 273–91; Henry F. Dobyns, *Their Number Became Thinned: Native American Population Dynamics in Eastern North America* (Knoxville: University of Tennessee Press, 1983), 11–16, 251–54, and passim; Linda A. Newson, "Old World Epidemics in Early Colonial Ecuador," in *"Secret Judgments of God": Old World Disease in Colonial Spanish America*, ed. Noble David Cook and W. George Lovell (Norman: University of Oklahoma Press, 1991), 84–112; Alida C. Metcalf, "The *Entradas* of Bahia of the Sixteenth Century," *Americas (Acad. Am. Francisc. Hist.)*, 2005, *61*, 373–400; John Hemming, *Red Gold: The Conquest of the Brazilian Indians* (Cambridge, Massachusetts: Harvard University Press, 1978), passim, esp. 142–43; Gary Warrick, "European Infectious Disease and Depopulation of the Wendat-Tionontate (Huron-Petun)," *World Archaeol.*, 2003, *35*, 257–75; C. Stuart Houston and Stan Houston, "The First Smallpox Epidemic on the Canadian Plains: In the Fur-traders' Words," *Can. J. Infect. Dis.*, 2000, *11*, 112–15; Reuben Gold Thwaites, ed., *The Jesuit Relations and Allied Documents: Travels and Explorations of the Jesuit Missionaries in New France, 1610–1791*, 73 vols. (Cleveland: Burrows Bros. Co, 1896–1901), 19, 89, 93, 185, 221, 223–31, and passim; William Bradford, *Of Plymouth Plantation, 1620–1647: The Complete Text*, ed. Samuel Eliot Morison (New York: Knopf, 1952), 270; Dean R. Snow, "Disease and Population Decline in the Northeast," in *Disease and Demography in the Americas*, ed. John W. Verano and Douglas H. Ubelaker (Washington, DC: Smithsonian Institution Press, 1992), 177–86; H. Ostermann, "The History of the Mission," in *Greenland*, 3 vols., ed. M. Vahl et al. (Copenhagen: C.A. Reitzel, 1928–1929), 3: 281; Hans Egede, *A Description of Greenland*. New ed. (London: A. & T. Allman, 1818); Louis Bobé, *Hans Egede, Colonizer and Missionary of Greenland* (Copenhagen: Rosenkilde and Bagger, 1952), 161–67; Finn Gad, *The History of Greenland*, Vol. 2, 1700–1782, trans. Gordon C. Bowden (Montreal: McGill-Queen's University Press, 1973), 2: 138–76; David Cranz, *The History of Greenland...*, 2 vols. (London: Brethren's Society for the Furtherance of the Gospel among the Heathen, 1767), *1*: 326–48; Noble David Cook, "Sickness, Starvation, and Death in Early Hispaniola," *J. Interdis. Hist.*, 2002, *32*, 349–86; Thomas M. Whitmore, *Disease and Death in Early Colonial Mexico: Simulating Amerindian Depopulation* (Boulder, Colorado: Westview Press, 1992); Massimo Livi Bacci, *Conquest: The Destruction of the American Indios* (Cambridge: Cambridge

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SMALLPOX LETHALITY

The likelihood of dying with a case of smallpox varies sharply with age. High in infancy, this risk diminishes to a low point between ages 5 and 14. Case fatality rates rise again in youth and adulthood. This pattern appears in reports of age-specific fatality rates for all smallpox variants. Severely lethal variants show the highest case fatality rates, but all show the same age pattern. This pattern is depicted in the two most reliable assessments of what is believed to have been variola major, one for three cities in West Prussia during an outbreak in 1796 and the other among unvaccinated cases from numerous outbreaks in India at the end of the smallpox eradication program there, in 1974–75 (Table 1). Everyone who had smallpox in the three West Prussian cities was an infant, a child, or a youth; that is, smallpox there was so intensively endemic that adults had already had it. That was no longer true in India in 1974–75. There people of all ages were susceptible.[15]

These data show that the overall fatality rate in an outbreak will depend on the ages of the people who fell sick. In Europe when epidemics recurred often, as they did every three or four years in London, crude case fatality rates were high because most victims were young children. Where epidemics occurred less often, spaced apart by ten or fifteen years, those rates were lower.

What matters most here is that, in ordinary circumstances, the susceptibility of everyone in a population to smallpox would modify the case fatality rate. Collections of crude case fatality rates from eighteenth-century Europe show an average overall lethality of about 15 percent, suggesting that smallpox attacked not just infants and very young children but older children as well.[16] Thus in the three West Prussian cities in 1796, the overall rate was 15.6 percent.

University Press, 2008), esp. 45–63; and Richard H. Frost, "The Pueblo Indian Smallpox Epidemic in New Mexico, 1898–1899," *Bull. Hist. Med.*, 1990, *64*, 417–45.

15. Other reports, such as Rao's important table of case fatality rates from Madras in the 1960s, typically provide data for hospital cases, which are known to have been a subset of more severe cases. A. R. Rao, *Smallpox* (Bombay: Kothari Book Depot, 1972), 137. This same age-pattern occurs in other variants of smallpox, although with lower rates at each age.

16. Creighton. *History of Epidemics in Britain*, 2, 518–19 and 544; and Peter Razzell, *The Conquest of Smallpox*: *The Impact of Inoculation on Smallpox Mortality in Eighteenth-Century Britain* (Firle, Sussex: Caliban Books, 1977), 116–34.

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TABLE 1

Age-Specific Case Fatality Rates in Variola Major

Age group	West Prussia	India
0–1	35.9	45.7*
1–4	19.0	
5–9	10.9	15.5
10–14	3.4	5.8
15–19	10.0	15.3
20–29	No cases	22.6
30–39		23.1
40–49		30.8
50+		28.9

*Cases in infants and young children may be underreported, making for too high a rate.

Sources: Paul Kübler, *Geschichte der Pocken und der Impfung* (Berlin: Hirshwald, 1901), 97; and R. N. Basu, Z. Jezek, and N. A. Ward, *The Eradication of Smallpox from India* (New Delhi: World Health Organization, 1979), 59 and 65.

Europeans of that century who reported about a smallpox epidemic among American Indians in which people of all ages were susceptible might have been struck by higher crude fatality rates, such as the overall rate for India in 1974–75: 26.5 percent.

Hospital data, which report about a subset of the more severe smallpox cases, generally show higher case fatality rates, but those report about a select population and cannot be used to assess fatality rates in a general population.[17] In a nonselect population of the sick in eighteenth-century Europe or twentieth-century Asia, it is difficult to conceive of circumstances that could produce case fatality rates higher than 35–45%, and those only if the epidemic was restricted to the very young.

Smallpox outbreaks limited to young children, as in London, had high case fatality rates. The higher the proportion of cases that occurred also in children aged five to fourteen, the more the case fatality rate in an outbreak dropped. That rate rose again when

17. For example, Russell Thornton, Tim Miller, and Jonathan Warren, "American Indian Population Recovery following Smallpox Epidemics," *Amer. Anthropol.*, 1991, *93*, 28–45, use hospital experience to represent the effect of smallpox in general populations.

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adults and older people were added to the case mix, as in India. However, case fatality rates from the general population experience in Europe and Asia rarely reach levels high enough to account for what is reported about smallpox in the New World. Those reports generally indicate high levels, often half of the population, even up to 90 percent. Those may have been exaggerated. What has prompted the search for additional factors that may explain not just high but devastating lethality in smallpox epidemics among American Indians is that observers so consistently, from 1520 to 1899, report rates higher than what would seem plausible from experience anywhere else.

STAGES FROM EXPOSURE TO DISEASE

The process of becoming sick differs from one disease to another in a series of stages: exposure, infection, immune response, clinical (or sometimes subclinical) sickness, and, in smallpox, widely varying severity in the clinical types of episodes. In smallpox, the process may advance from one stage to the next, moving a susceptible person toward a clinical case evident by its signs and symptoms, or it may be interrupted at any point so that the person escapes sickness.[18] Close and prolonged contact with a person in the infective stage of smallpox accounts for most new cases in susceptible people. Public health advice warned against close contact with the sick in the nineteenth century. For smallpox in the period 1500–1800 children continued to visit sick friends, parents nursed sick family members, and friends and relatives of all ages visited the sick; these things happened in Europe, among people of European background in the New World, and among American Indians.

Up to about 1960, medical texts typically referred to smallpox as highly contagious.[19] Later studies showed that the proportion of susceptible people who developed disease was lower for smallpox

18. This section draws on Joseph J. Esposito and Frank Fenner, "Poxviruses," in *Fields Virology*, 4th ed., 2 vols., ed. David M. Knipe et al. (Philadelphia: Lippincott, Williams, & Wilkins, 2001), 2: 2885–86, 2895; Hua Jiang and Frederick C. S. Wang, "Poxvirus Infection in Humans," *Encyclopedia of Life Sciences*, available at http://mrw.interscience.wiley.com/emrw/9780470015902/els/article/a0002243/current/pdf (accessed 4 February 2010); and Thomas Mack, "A Different View of Smallpox and Vaccination," *N. Engl. J. Med.*, 2003, *348*, 460–63.

19. See, for example, Saul Krugman and Robert Ward, *Infectious Diseases of Children* (St. Louis: Mosby, 1958), 225.

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than for measles, chickenpox, or influenza. A. R. Rao, an experienced clinician working in Madras from the 1950s to the 1970s, emphasized the distinction between infectiousness and infectiveness. Many people with smallpox shed viable viruses (they may be infectious) without managing to infect others (without being infective). He found that smallpox cases were infectious until the last scab healed, but infective only for part of that period; most secondary cases occurred from contact with the sick person on the fourth to seventh day after the onset of that person's illness (the sixth to the ninth day after the onset of fever), and none after the thirteenth day of illness.[20] Thus smallpox is highly infectious but not highly infective. Moreover, at the Madras hospital patients with the most and least serious clinical types of smallpox, respectively, hemorrhagic and modified in Rao's terminology, transmitted the disease less often than patients with flat or ordinary smallpox. Rao speculated that patient behavior accounted for the differences. Hemorrhagic smallpox produced fewer secondary cases because of its alarming symptoms (bleeding into the skin, rapid progress usually to death), which in Madras led family members to avoid contact at home and to take sick family members to the hospital. As a result, fewer susceptible people were exposed. At the opposite end of the transmission spectrum, children aged five to fourteen were the likeliest to infect others because they were rarely confined to bed and received more attention from other family members than did younger children with smallpox.[21]

Smallpox was most often transmitted not from skin lesions but when a susceptible person breathed in virus-bearing mucous droplets from the exhalations of a sick person who coughed, sneezed, or talked, releasing matter from lesions in the upper respiratory system and the mouth, which break down earliest.[22] Variola entered the body in the mouth, pharynx, or respiratory tract.

Since mucous droplets emitted are heavier than the bacteria-bearing droplets coughed or sneezed out by someone with

20. Rao, *Smallpox*, 76.

21. Ibid., 77 and 112–19. People with modified or mild smallpox were less likely to transmit the disease because they developed only mild lesions in the nasal and buccal mucous membranes.

22. G. Bras, "The Morbid Anatomy of Smallpox," *Documenta de medicina geographica et tropica*, 1952, *4*, 303–51, reports on the location of lesions in the mucosal system.

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tuberculosis, they rarely circulate far. In 1927, Murray Cowie suggested a radius of three feet as the infective space, and ventured the opinion that actual contact, rather than respiration, is the principal mode of transmission.[23] Rao in 1972 defined contact to mean three or four feet, with a proximity of twelve inches or less the likeliest to ensure infection.[24] Merely living in the same compound or dwelling did not assure transmission. In outbreaks in rural West Pakistan in 1968–70 among susceptible people who lived in closely spaced dwellings of one or two rooms within the same compound, only 70 percent fell sick.[25] Lingering at the bedside or in other face-to-face contact with a sick person made transmission likeliest. Susceptible people who made frequent but brief visits to a sick room were less likely to contract smallpox than those who remained at the bedside for longer periods. Sleeping in the same bed or small room exposed a susceptible person the most efficiently.[26]

A single variola virion may be enough to cause smallpox, but most episodes are thought to have occurred after a larger dose of viral matter. After penetrating the mucosal surface, variola quickly replicated in stunningly large numbers beginning early after infection, first in the respiratory mucosa, and then in lymph nodes, the spleen, and bone marrow before settling in the blood vessels of the skin and mucous membranes, where lesions began to form. Most typically replication far outpaced the build-up of an innate immune response.

Thus a high proportion of people infected through the mouth with a small or large dose of variola went on to become sick. Paul Fine describes smallpox, with measles, as one of the most pathogenic diseases in that more than 90 percent of people infected with

23. D. Murray Cowie, "Smallpox," in *A Text-Book of Medicine*, ed. Russell L. Cecil (Philadelphia: W.B. Saunders, 1927), 296–308.

24. Rao, *Smallpox*, 91; and A. W. Downie et al., "The Recovery of Smallpox Virus from Patients and Their Environment in a Smallpox Hospital," *Bull. World Health Org.*, 1965, *33*, 615–22.

25. Gordon G. Heiner, Nusrat Fatima, and Fred R. McCrumb, Jr., "A Study of Intrafamilial Transmission of Smallpox," *Am. J. Epidemiol.*, 1971, *94*, 316–26. M. K. Mukherjee, J. K. Sarkar, and A. C. Mitra, "Pattern of Interfamilial Transmission of Smallpox in Calcutta, India," *Bull. World Health Org.*, 1974, *51*, 219–25, report that in compounds where family members living in a single room mingled freely with other residents of the compound, the risk of transmission within the family was not greater than to others in the compound.

26. Rao, *Smallpox*, 116.

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this virus developed a clinical case.[27] People who have had smallpox previously are able to mount an adaptive immune response quickly, thus avoiding becoming sick a second time.

The size of the dose is believed to have played a role in the duration of the incubation period and is known to have affected the clinical type of smallpox,[28] with larger doses producing more severe types.[29] Genetic factors and the state of the host's immune system are also believed to have influenced how cases developed and were resolved.[30] Some poxviruses, perhaps including variola, seem to have the capacity to modify the immune response in comparatively rapid time in evolutionary terms.[31] In the timescale of an individual infection, Stanford and team describe the outcome of infection as the product of interaction between the host's immune response and the virus' mechanisms of evasion.[32] Poxviruses all have a comparative disadvantage in their large size, which makes them easier targets for an immune response. To address this disadvantage poxviruses have developed ways to counter host defenses. "Many poxviruses [but not necessarily variola] particularly target the innate and inflammatory portion of the host response thus ensuring successful establishment of infection."[33] Based on work with some other poxviruses, but not variola, McFadden suggests that individuals and human groups may vary in their genetic capacity to respond to some of the devices used by poxviruses.[34]

These findings and hypotheses suggest that smallpox was more lethal in the young because of incompletely developed immune

27. Paul E. M. Fine, "The Interval Between Successive Cases of an Infectious Disease," *Am. J. Epidemiol.*, 2003, *158*, 1039–47.

28. Ibid.

29. P. B. Jahrling et al., "Exploring the Potential of Variola Virus Infection of Cynomolgus Macaques as a Model for Human Smallpox," *Proc. Natl Acad. Sci. USA*, 2004, *101*, 15196–200, available at http://www.pnas.org/content/101/42/15196.full.pdf+html. (Accessed 4 February 2010.)

30. World Health Organization, Advisory Committee on Variola Virus Research, Reports, Geneva, various dates, which may be accessed, as of 31 December 2008, at http ://www.who.int.csr.disease/smallpox/research/en/index.html. (Accessed 4 February 2010.)

31. Stefan Rothenburg et al., "Rapid Evolution of Protein Kinase PKR Alters Sensitivity to Viral Inhibitors," *Nat. Struct. Mol. Biol.*, 2009, *16*, 63–70.

32. Marianne M. Stanford et al., "Immunopathogenesis of Poxvirus Infections: Forecasting the Impending Storm," *Immunol. Cell Biol.*, 2007, *85*, 93–102.

33. Ibid., 94.

34. Grant McFadden and Michele Barry, "How Poxviruses Oppose Apoptosis," *Semin. Virol*, 1998, *8*, 429–42.

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response, and in the old because of impaired immune response. However, in some hosts of any age, even vaccinated hosts, an immune response impaired by actions of the virus or by other factors could fail to slow viral replication, leading to a quick build-up of high viral levels, severe sickness, and death.

Experience with smallpox in the 1960s and 1970s, and laboratory findings made then and since, indicate that smallpox was likeliest to be transmitted when a susceptible individual was in close and prolonged contact with a sick person. It was likeliest to develop into a severe, life-threatening episode with prolonged and close exposure to any but a mild clinical type. Moreover, it was likeliest to result in death either because the dose was large or the immune response impaired. Sleeping in the same room provided efficient conditions for transmission of smallpox, and for universal, or virtually universal, infection.[35]

SMALLPOX AND SOMETHING ELSE

Historians have tried to identify which aggravating factors may have contributed most in making American Indians so vulnerable to smallpox.[36] This section assesses the factors that have been suggested in the light of new and previously unconsidered evidence, and adds two hypotheses to the discussion.

Familiar Hypotheses

Social disruption Paul Kelton gives the most recent formulation for this hypothesis, writing about epidemics in general rather than specifically about smallpox: "With everyone succumbing to infection, basic social services broke down; sick individuals were left without food, water, and care, making survival even more difficult."[37] Many descriptions of New World epidemics refer to smallpox striking so many people at the same time that there was no one left to meet

35. For modern evidence, see Heiner, Fatima, and McCrumb, Jr., "Intrafamilial Transmission of Smallpox."

36. David S. Jones, "Virgin Soils Revisited," *William Mary Q.*, 2003, *60*, 703–42; McCaa, "Spanish and Nahuatl Views"; Elizabeth A. Fenn, *Pox Americana: The Great Smallpox Epidemic of 1775–82* (New York: Hill & Wang, 2001), 12–13; and Paul Kelton, *Epidemics and Enslavement: Biological Catastrophe in the Native Southeast, 1492–1715* (Lincoln: University of Nebraska Press, 2007), 42–46 and passim, survey hypotheses.

37. Paul Kelton, "Avoiding the Smallpox Spirits: Colonial Epidemics and Southeastern Indian Survival," *Ethnohistory*, 2004, *51*, 45–71, 46.

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the basic needs of the sick, to bring water, to gather or prepare food, or to give care.[38]

In smallpox, the period from the onset of fever to recovery lasts typically for twenty to twenty-four days, giving a fairly broad opportunity for people in a single small settlement to be sick at once, at least for a few days. After the arrival of a person who was or who became sick, smallpox was probably transmitted in a sequence of infections beginning in the dwelling where that person slept, infecting first those sleeping next to the infective case, spreading to others sleeping in the same room, and then to visitors from other dwellings who spent enough time within two or three feet of the infective person. In a small settlement with only a few dwellings, everyone might have been infected within a week, being sick during overlapping periods lasting as long as two weeks.[39]

People are likelier to be sick all at once with measles than with smallpox. However, speedier recovery—measles persists for a week to ten days—means that some people would soon be able to resume at least the simplest activities of providing water and food to the sick. Because it persists for about three weeks, smallpox fits better as a disease in which sicknesses among people would overlap long enough to aggravate disease effects.

However, smallpox is also known as a malady in which some of the sick alternated from day to day in how badly they felt and in levels of activity; on some days they felt well enough to go outside and perform easy tasks. In the last days of an episode, when the pustules were drying and scabbing, many people resumed activities. People with mild clinical types, which in modern experience were the most common, may never have been disabled from ordinary activities. Many descriptions of smallpox refer to people in some part of the eruptive stage going to markets and to church. Most of the sick could not perform physically demanding tasks, such as hunting and tending crops, while sick, but would have been able to

38. This is mentioned also as a factor in the Icelandic epidemic of 1707–1709. Jón Steffensen, "Smallpox in Iceland," *Nord Medicinhist Arsb.*, 1977, *41*, 41–56, 49.

39. Richard Frost ("Pueblo Indian Smallpox Epidemic") describes the 1898–1899 epidemic in some settlements in New Mexico in a way that suggests slower transmission, and therefore less overlapping in sickness. Reports from school teachers and nurses appointed by federal authorities indicate that in each settlement the outbreak began with a single case, which then infected four or five others, and those some other people, until the outbreak exhausted itself.

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resume some work within days if they had enough food to regain strength.[40]

For American Indians with more severe cases what probably mattered most for the twelve- to fourteen-day period of disability was access to water. Treating patients in Madras in the 1960s and 1970s, Rao acknowledged that therapy was at best palliative. He could administer antibiotics to prevent secondary bacterial infections, but using antibiotics did little or nothing to change either the outcome of cases or the well-being of patients. Secondary infections and bronchopneumonia, which antibiotics were expected to treat, remained common because they were viral. Rao could also order nursing care and a nutritious diet.[41] He and his colleagues gave sedatives to patients with mild cases, and for those with early hemorrhagic cases, in which patients sense impending death, they turned to hypnotic drugs. For children, who tended to scratch their lesions more than adults did, Rao advised medications to reduce itching. In confluent cases, it was possible to relieve skin tension by applying an oil preparation, making those patients more comfortable and reducing the odor.

For Rao, the most important treatment was good nursing, meaning kind words, moral support, and cleansing the patient. Clean the mouth to deter inflammation of the salivary glands. Bathe the eyes daily with a saline lotion and give antibiotics to reduce the likelihood of blindness. Clean the body to deter bedsores or, taking advantage of local resources, put a full-sized banana leaf smeared with oil on top of the sheet to prevent the patient's sores from adhering to the sheet. Then change that at least daily. Clean the throat of its sticky sputum, if necessary with a suction device. Give the patient plenty of fluids and any foods that can be swallowed. (People with severe cases of smallpox often have lesions in their throat that make eating difficult, and they may refuse food

40. Rao, *Smallpox*; and C. W. Dixon, *Smallpox* (London: Churchill, 1962) discuss the different clinical types of smallpox in detail. For reports about an individual case in which the patient, Louis XV of France, alternated periods of activity with disability, see Pierre Darmon, *La variole, les nobles, et les princes; La petite vérole mortelle de Louis XV* (Brussels: Editions Complexe, 1989); Michel Antoine, *Louis XV* (Paris: Fayard, 1989), 982–92; and Catriona Seth, *Les rois aussi en mouraient: Les lumières en lutte contre la petite vérole* (Paris: Desjonquères, 2008), 243–53.

41. Rao, *Smallpox*, 54–59. Also Saul Krugman and Robert Ward. *Infectious Diseases of Children* (St. Louis: Mosby, 1958), 234–35.

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and drink.) Since convalescent patients in the latter stage of disease are usually hungry, feed them well. All of that relieved the discomfort and pain of smallpox, but had no observable effect on whether the patient recovered or died.

Rao's assessment of care giving suggests that what mattered was not nursing, in the sense of medical attendance, but care giving in the sense of meeting the most basic need of providing water. The period in which the sick among American Indians were unable to prepare food for themselves, much less gather it, was not long enough to have produced starvation in adequately or even marginally nourished people.[42] However, the period during which everyone or nearly everyone who remained in a settlement may have been too sick to collect water, or to give it to the sick, was long enough to allow dehydration, which is especially hazardous for children.[43]

Flight from the sick, documented in Greenland in 1733 and in many other outbreaks, or from the dead; resignation and fatalism; and abhorrence of the sick, whose foul odor in the pustular stage is a classic manifestation, all may add some effect to situations in which the sick were untended or too little tended. Treatments that Indians used for smallpox may also have done more harm than good. Some groups put the sick in sweathouses. European observers often mentioned that Indians, when feverish, used cold baths, or plunged into cold water, seeking relief. The Europeans believed those things to be harmful, which may be so, but those same Europeans believed the therapies they used for smallpox to be helpful, which was not true. In Brazil, the Jesuits let blood and medicated their Indian smallpox patients, presumably to ill effect, but they did also wash the sick person's sores with warm water.

Denial of basic care giving must have aggravated smallpox mortality. What is needed better to assess how much that may have contributed to smallpox mortality among American Indians is more information about how people reacted to sickness in a settlement.

42. McCaa, "Spanish and Nahuatl Views," 420–21 and 426, maintains that many people may have starved. However, in later work ("Revisioning Smallpox"), he sees lack of water and dehydration as likelier problems.

43. Arthur C. Aufderheide, Conrado Rodriguez-Martin, and Odin Langsjoen, *The Cambridge Encyclopedia of Human Paleopathology* (New York: Cambridge University Press, 1998), 206.

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Was flight typical? Were those not sick unable or unwilling to give water to the sick? Were the sick who recovered too disheartened by their episode, or too weak, to give basic care to secondary and tertiary cases?

Nutrition This hypothesis, as argued recently by David S. Jones, is that "malnutrition increases susceptibility to infection. Some vitamin deficiencies cause skin breakdown, eroding the first barrier of defense" and "protein deficiencies impair both cellular and humoral" immune responses. "Malnutrition during infancy and childhood has particularly devastating effects on subsequent immune function." Such impairments are known to produce higher mortality in measles and chickenpox.[44]

Twentieth-century medical commentary has avoided strong statements about a nutrition-smallpox link. Rao does not discuss nutrition as a factor in smallpox. C. W. Dixon, another experienced clinician and author of a standard text on smallpox, mentions nutrition as a likely factor only in certain complications, associates gross nutritional deficiency with blindness after smallpox, and suggests that nutritional status in nineteenth-century England was generally poor enough to allow an infection of the lymph vessels to develop at vaccination sites by slowing the build-up of an immune system response. Fenner et al. identify the nutritional status of hosts as a likely factor in the outcome of smallpox cases, and report that WHO epidemiologists working in India during the eradication campaign had the impression that cases were more severe and deaths more frequent in malnourished people.[45] However, they did not find evidence to assess these speculations.

An impaired immune response is known to produce more severe cases and more frequent death in some infectious diseases. R. K. Chandra, who regularly summarized findings about the nutrition-severity link from the 1970s through the 1990s, reported that malnourished people have more severe cases of measles and tuberculosis, but that in some other viral and bacterial diseases the effect of poor nutrition is minimal or undetected. Chandra suggested general links between famines and epidemic disease, and a specific

44. Jones, "Virgin Soils Revisited," 135.

45. Dixon, *Smallpox*, 92–93, 95, and 144–45; and F. Fenner et al., *Smallpox and Its Eradication* (Geneva: World Health Organization, 1988), 176 and 196.

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link between protein-energy malnutrition, a term coined to encompass marasmus (muscle wasting) and kwashiorkor (a swollen abdomen), and famine.[46] In a more recent review, Marcos, Nove, and Montero report that cell-mediated immunity, the complement system, phagocyte function, cytokine production, the mucosal secretory antibody response, and antibody affinity all behave abnormally under nutritional stress as severe as protein-calorie malnutrition, and with severe micronutrient deficiencies.[47]

Severe protein-calorie malnutrition, studied in some populations in developing countries during the second half of the twentieth century, is known to be associated with metabolic derangements that inhibit the growth and functioning of lymphocytes, which as natural killer cells, T cells, and B cells combat antigens including those of smallpox. Some studies find some of these impairments in many or most severely malnourished test subjects, others in only a fraction.[48] A deficit in immunoglobulin production by the adaptive immune system might mean that viral replication would quickly swamp the immune response. All this suggests the possibility that some degree of severe malnutrition might make smallpox more lethal.

Toward the end of the WHO smallpox eradication campaign, research teams working in India and Nigeria studied immune response after vaccination against smallpox. Vaccination infects with another orthopoxvirus, vaccinia, in order to induce protection against variola. WHO authorities and some other observers worried that vaccination might do more harm than good in poorly nourished children.

Reddy et al. found that severely malnourished children showed immune response impairments, but that children with mild to moderate protein-calorie malnutrition, defined as 60–80% of the

46. R. K. Chandra, "Nutrition and Immunology: From the Clinic to Cellular Biology and Back Again," *Proc. Nutr. Soc.*, 1999, *58*, 681–83; R. K. Chandra, "Nutrition and the Immune System: An Introduction," *Am. J. Clin. Nutr.*, 1997, *66*, S460–S463; and Ranjit Kumar Chandra, "Protein-Energy Malnutrition and Immunological Responses," *J. Nutr*, 1992, *122*, 597–600.

47. A. Marcos, E. Nove, and A. Montero, "Changes in the Immune System Are Conditioned by Nutrition," *Eur. J. Clin. Nutr.*, 2003, *57*, Suppl. 1, S66–S69.

48. See, for example, Charlotte G. Neumann et al., "Immunologic Responses in Malnourished Children," *Am. J. Clin. Nutr.*, 1975, *28*, 89–104. This article reports impaired lymphocytes in five of twenty-seven severely malnourished children, but not in any moderately malnourished subjects.

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Indian Council of Medical Research standard of weight for age, showed no impairment in immune response. K. Saha et al. studied the immune response to smallpox revaccination in "chronically starved" adults all of whom had been vaccinated in childhood. The cellular immunity response was "remarkably poor" in the badly nourished group compared with the control group, and the immune system spectacularly unresponsive to many antigens. Those undernourished subjects had lost weight gradually over six to eighteen months, and showed an average weight 35–40% of the Indian norm. However, vaccination with live vaccine, considered a more robust challenge than freeze-dried vaccine, was effective and harmless despite the many immune system impairments observed in the thirty-one severely malnourished adult males in this study.

Considering whether to administer measles and smallpox vaccinations in Nigeria in the late 1970s, during the Biafra war, Ifekwunigwe et al. tested 111 Nigerian children mostly aged under five showing no blood system evidence of prior disease or immunization. The ninety-two children judged to be mildly, moderately, or severely malnourished showed an immune response to vaccination challenges equal to or better than that of nineteen control subjects with normal nutritional status. All three research teams recommended vaccination even of the most poorly nourished people.[49] (Fenner et al. acknowledge a failure to find data on this issue but do not cite any of the sources just discussed.) Other research indicates that atypically heavy doses of an infectious agent may combine with severe protein-calorie malnutrition to produce more severe cases of an infection.[50]

Even though it is also an orthopoxvirus, vaccinia may not accurately capture the effects of malnutrition in cases of variola. However, the outcome of these tests with vaccinia does mean that a link between malnutrition and variola has not yet been demonstrated. Current knowledge suggests that immune response

49. Vinodini Reddy, C. Bhaskaram, and N. Raghuramulu, "Immunological Responses in Malnourished Children," *Indian Pediatr.*, 1977, *14*, 255–58; K. Saha et al., "Undernutrition and Immunity: Smallpox Vaccination in Chronically Starved, Undernourished Subjects and Its Immunologic Evaluation," *Scand. J. Immunol.*, 1977, *6*, 581–89; and Aaron E. Ifekwunigwe et al., "Immune Response to Measles and Smallpox Vaccinations in Malnourished Children," *Am. J. Clin. Nutr.*, 1980, *33*, 621–24.

50. Lars Å. Hanson. *Immunobiology of Human Milk*: *How Breastfeeding Protects Babies* (Amarillo, Texas: Pharmasoft, 2004), 60, not specifically discussing variola.

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impairments likely to lead to more severe cases of smallpox occur at most in a fraction of the most poorly nourished. In India in the late 1970s, 1–2% of children were judged to suffer protein-calorie malnutrition, and a fraction of those to suffer immune response impairments.

Some scholars have suggested that American Indians suffered from protein-calorie malnutrition. How widespread such malnutrition may have been in the period 1500–1800 is thus an issue for assessing the impact of smallpox and other diseases. Protein-calorie malnutrition and protein malnutrition produce their own signs beyond immune system impairment, which include persisting weight loss, anemia, slow wound healing, eventual muscle atrophy, and a lack of enough energy to perform usual daily tasks. These and other signs provide specific things to look for in descriptions of Indian life, over and above skeletal evidence, which sometimes indicates anemia and other nutritional deficits.[51]

Greenlanders, who suffered smallpox in a severe epidemic, subsisted on a diet of some roots and seaweed, but mostly birds, fish, and sea mammals. They were overweight for their heights, and sometimes had scurvy, but are not reported to have suffered protein malnutrition. Dietaries of North American Indians suggest a more balanced diet, but periods during the year when food was in short supply. Seasonal food shortages also provide an opportunity to look for specific evidence: did smallpox epidemics that coincided with seasonal food shortages produce higher lethality?

Micronutrient deficiencies may also weaken the immune response or impair the capacity of the skin or the mucosal system to impede pathogen entry. Little evidence exists about specific deficiencies that may interact with variola. Archaeological reconstruction of Indian diets from food remains a field that is accumulating new information, may produce leads about deficiencies.[52] However, it will also be necessary to discover more about how specific deficiencies

51. See, e.g., Phillip L. Walker and Russell Thornton, "Health, Nutrition, and Demographic Change in Native California," in *The Backbone of History: Health and Nutrition in the Western Hemisphere*, ed. Richard H. Steckel and Jerome C. Rose (Cambridge: Cambridge University Press, 2002), 506–23, esp. 511–19.

52. For example, see Kristen J. Gremillion, "Report on Plant Remains from the Berry and McDowell Sites," in *Catawba Valley Mississippian: Ceramics, Chronology, and Catawba Indians*, ed. David G. Moore (Tuscaloosa: University of Alabama Press, 2002), 299–313; and John E. Byrd, *Tuscarora Subsistence Practices in the Late Woodland Period: The*

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impair the mucosal system, and how mucosal impairment interacts with infection.

Another body of scholarly discussion seeks to know whether smallpox caused nutritional deficits serious enough to stunt growth in children in nineteenth-century England.[53] It seems certain that many children ate little during smallpox episodes, at least for the initial ten days to two weeks after the onset of fever. What is uncertain is how to track long-term effects of such brief nutritional gaps, and how to separate nutritional problems, including micronutrient deficiencies, in the unvaccinated poor from those in vaccinated and unvaccinated elites. Thomas Sydenham, treating newly more lethal cases of smallpox in London in the late 1660s, suggested that the manner of living among the elite made them more prone to die when they had smallpox than people from other social ranks.[54] Other European commentators typically found no socioeconomic stratification of people sick or dead from smallpox until the nineteenth century, when a readier uptake of vaccination among elites gave their children an advantage that might, without understanding the vaccination issue, appear to result from better nutrition.

For communicable diseases in general, modern research suggests that a sudden food shortage may change patterns of behavior in ways that make it likelier that infectious diseases will spread, such as when hungry rural people who have not been exposed to a disease go to cities where that disease is endemic in search of food or work. In famines in nineteenth-century India, the rural poor sometimes migrated to cities looking for work and food but exposing

Zooarchaeology of the Jordan's Landing Site (Raleigh: North Carolina Archaeology Council, 1997).

53. See Hans-Joachim Voth and Timothy Leunig, "Did Smallpox Reduce Height? Stature and the Standard of Living in London, 1770–1873," *Econ. Hist. Rev.*, 1996, *49*, 541–60; Timothy Leunig and Hans-Joachim Voth, "Smallpox Did Reduce Height: A Reply to Our Critics," *Econ. Hist. Rev.*, 1998, *51*, 372–81 (which cites an initial set of critics); Deborah Oxley, "'The Seat of Death and Terror': Urbanization, Stunting, and Smallpox," *Econ. Hist. Rev.*, 2003, *56*, 623–56; Timothy Leunig and Hans-Joachim Voth, "Comment on 'Seat of Death and Terror,'" *Econ. Hist. Rev.*, 2006, *59*, 607–16; and Deborah Oxley, "'Pitted but Not Pitied' or, Does Smallpox Make You Small?" *Econ. Hist. Rev.*, 2006, *59*, 617–35.

54. R. G. Latham, ed., *The Works of Thomas Sydenham*, 2 vols. (London: for the Sydenham Society, 1848–1850), I: 142.

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themselves to smallpox.[55] So, too, did nomads in Ethiopia in the 1970s faced with drought; their migrations in search of water carried smallpox into Somalia in 1975 and 1976.[56]

In sum, historians sometimes argue that malnutrition increases the likelihood of infection and death from infectious diseases in general. Medical evidence shows that this interaction varies from disease to disease. For smallpox, the most experienced clinicians, Dixon and Rao, do not suggest a general link. Tests with vaccinia, a closely related orthopoxvirus, find damage in a small fraction of the most severely malnourished in two settings, India and war-torn Nigeria in the 1960s, where chronic and severe malnutrition were common. The evidence now available holds out some possibilities for further research, but does not support the hypothesis that nutritional deficits produced immune response impairments that aggravated smallpox among American Indians. Poor nutrition is unlikely to have contributed to high smallpox lethality in the Americas not because Indians were well nourished but because smallpox has not been shown to have interacted with poor nutrition to undermine the immune response. Food shortages may, however, have prompted population movements that spread smallpox more widely than would otherwise have occurred, adding to mortality from this disease.

Genetic impairment Speculations among historians about whether American Indians were more genetically susceptible to smallpox rest mainly on the ABO hypothesis. Investigating a smallpox outbreak in rural India in 1965–66, Vogel and Chakravartti found that smallpox infections, severe cases, and deaths were all more common in the blood groups A and AB than in O and B. Other researchers working in Brazil and India failed to replicate that finding, and a study of smallpox patients at the Madras Infectious Diseases

55. David Arnold, "Social Crisis and Epidemic Disease in the Famines of Nineteenth-century India," *Soc. Hist. Med.*, 1993, *6*, 385–404.

56. Z. Jezek et al., *Smallpox Eradication in Somalia* (Geneva: World Health Organization, 1979), 51, 54. Fenner et al., *Smallpox*, 164, report that "WHO epidemiologists working in Ethiopia and Somalia noticed that variola minor [the variant prevalent there] was much more severe in malnourished than in well-nourished infants." Jezek et al., epidemiologists working in Somalia, do not mention this in their detailed account. In 1977, they report 3,229 cases and 12 deaths, for a case fatality rate of 0.37 percent. Nor is this mentioned in Ato Yemane Tekeste et al., *Smallpox Eradication in Ethiopia* (Geneva: World Health Organization, 1979).

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Hospital found no association between blood group and disease severity. Without apparently knowing about the replication failures, S. Adalsteinsson drew on this hypothesis to explain why the current Iceland population has a high frequency of blood group O and a low frequency of A even though most of the original settlers came from Norway and therefore from a population with a high proportion of blood group A.[57]

If the ABO hypothesis has merit, then it would seem to follow that West Europeans, where group A is common, would have been more at risk of smallpox than Asians, where group B is more common. However, most commentators indicate that smallpox was more often lethal in Asia than in Europe. The standard authorities on the geography of blood groups, Mourant, Kopeć and Domaniewska-Sobczak, report that American Indians in Mexico already had a low frequency of group A before the arrival of Europeans.[58]

American Indians are known to have responded to vaccination with vaccinia in the same way as Europeans.[59] That makes it unlikely that American Indians harbored any generalized orthopoxvirus immune response deficiency.[60] Future research may, however,

57. F. Vogel and M. R. Chakravartti, "ABO Blood Groups and Smallpox in a Rural Population of West Bengal and Bihar (India)," *Humangenetik*, 1966, *3*, 166–80; H. Krieger and A. T. Vicente, "Smallpox and the ABO System in Southern Brazil," *Hum. Hered.*, 1969, *19*, 654–57; and A. W. Downie et al., "Smallpox Frequency and Severity in Relation to A, B and O Blood Groups," *Bull. World Health Organ.*, 1965, *33*, 623–25. (Downie et al. reacted to a 1960 article on this issue.) The most recent work on this topic finds that associations of blood groups with disease are accepted but not yet well understood; it does not revisit the smallpox ABO case. George Garratty, "Blood Groups and Disease: A Historical Perspective," *Transfus. Med. Rev.*, 2000, *14*, 291–301; and George Garratty, "Association of Blood Groups and Disease: Do Blood Group Antigens and Antibodies Have a Biological Role?" *Hist. Philos. Life Sci.*, 1996, *18*, 321–44. On Iceland, see S. Adalsteinsson, "Possible Changes in the Frequency of the Human ABO Blood Groups in Iceland Due to Smallpox Epidemics Selection," *Ann. Hum. Genet.*, 1985, *49*, 275–81.

58. A. E. Mourant, Ada C. Kopeć, and Kazimiera Domaniewska-Sobczak, *The Distribution of the Human Blood Groups and Other Polymorphisms*, 2nd ed. (London: Oxford University Press, 1976), 117, 119–20.

59. Aufderheide, Rodriguez-Martin, and Langsjoen, *Cambridge Encyclopedia of Human Paleopathology*, 206.

60. For some other possibilities dealing with interactions between viruses and elements in the immune response, see also Rothenburg et al., "Rapid Evolution of Protein Kinase PKR"; Eun Joo Seo et al., "Protein Kinase PKR Mutants Resistant to the Poxvirus Pseudosubstrate K3L Protein," *Proc. Natl Acad. Sci. USA*, 2008, *105*, 16894–99; Nels Elde et al., "Protein Kinase R Reveals an Evolutionary Model for Defeating Viral Mimicry," *Nature*, 2009, *457*, 485–89; and Bruce T. Seet et al., "Poxviruses and Immune Evasion," *Ann. Rev. Immunol.*, 2003, *21*, 377–423.

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discover genetic characteristics in Indians and other populations that give orthopoxviruses either an advantage or a disadvantage in human infections.

Genetic homogeneity Francis Black found markedly less heterogeneity "in [the] highly polymorphic loci that control the immune system, the Class I and II histocompatibility antigens (MHC) and the immunoglobulin allotype genes" among American Indians than in other populations.[61] Once adapted to one person's immune response, a virus required no further adaptation in a new host, and could transform an infection into disease with less resistance from the host's immune response.

Black's evidence applies specifically to measles. He extrapolated from measles to smallpox without explaining why a characteristic of an RNA virus, measles, should apply to a DNA virus, smallpox. RNA viruses are known to be unstable and to adapt to hosts in ways important for the capacity of the virus to infect and cause disease after infection. DNA viruses including variola are comparatively stable.[62] It is also the case that the size of the infective dose in measles does not affect the severity of measles symptoms, according to Black, but does in smallpox.

Black's argument suggests that members of the same family are likelier to die when they pass smallpox from one to another, whereas a smallpox infection from a stranger is likely to produce a less virulent episode. Yet even early authorities, including Sydenham writing in 1682, recognized that the severity of smallpox cases varied from person to person within an epidemic, even within the same family. Rao underscored the finding that people do not transmit their own clinical type of smallpox. Black's extrapolation from measles to smallpox is unconvincing.

Additional Hypotheses

Host behavior in ordinary times The 1774 epidemic in the market town of Chester, England, began when some 2,300 residents were

61. Francis L. Black, "An Explanation of High Death Rates among New World Peoples When in Contact with Old World Diseases," *Perspect. Biol. Med.*, 1994, *37*, 292–307, 296.

62. Babkin and Shchelkunov, "Molecular Evolution of Poxviruses," provide estimates of the rate of adaptation in each virus.

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susceptible to smallpox out of a population of about 14,800, and ended with 1,060 susceptible persons in a population numbering 14,713.[63] John Haygarth, who practiced medicine in Chester, reported 1,385 cases during the epidemic, from which it appears that about 60 percent of the susceptible population got smallpox (i.e., 1,385 cases among 2,300 susceptibles, including infants born during 1774). Among American Indians in the each initial outbreak in each area, everyone was susceptible. What proportion became sick?

As reported above, more than 90 percent of people infected with smallpox go on to develop a clinical case. What proportion of susceptible people are exposed intensively enough to be infected? In Chester in 1774, many susceptibles escaped infection even in a major epidemic.

Certain features of life among American Indians, common to many but not all communities, assisted the transmission of smallpox from person to person and place to place. In Mexico and among the Iroquois and Huron in Canada, groups of people regularly slept and ate together in single-room structures, exposing large segments of the settlement to transmission within a single dwelling. At individual settlements in Mexico in 1520, "they all fell ill at a stroke."[64] Among Indians living near Quebec, the typical village was composed of closely spaced longhouses, each shared by two families and sheltering thirty to forty people, the whole settlement surrounded by a palisade.[65] Jesuit testimony about the Huron shows also that they visited the sick without any fear of contagion. Sleeping in the same room and visiting the sick both made smallpox transmission within a community more efficient.

These examples suggest only some of the living conditions that provided an opportunity for more frequent close and prolonged contacts between the sick and the still uninfected, and therefore for more intensive exposure, than in Europe. In Chester, as elsewhere in

63. J. Haygarth, "Observations on the Population and Diseases of Chester, in the Year 1774," *Phil. Trans. Royal Soc. London*, 1778, *67*, 131–54, assuming no net migration and using Haygarth's report of baptisms and burials to work back to the pre-epidemic population estimate.

64. McCaa, "Spanish and Nahuatl Views," 420.

65. Ibid., 412; McCaa, "The Nahua *Calli* of Ancient Mexico"; Warrick, "European Infectious Disease and Depopulation of the Wendat-Tionontate"; and Louis Henry Morgan, *Houses and House-life of the American Aborigines* (1881; repr., Chicago: University of Chicago Press, 1965), 258–68.

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Europe, most households occupied multi-room dwellings. Nor did people live in compounds, of the type common in West Pakistan in the 1960s and 1970s, in which one- and two-room dwellings were grouped around a common open space. What seems to matter for American Indians is how often people in the same community slept, ate, or engaged in other activities that put them in close proximity to one another. Did Indians continue to sleep in the same room after others in that space fell sick? Who tended the sick?

In typical outbreaks in locales where this disease was endemic, smallpox spread slowly through a community as each sick person communicated the virus in the early cycles of transmission to an average of one and a half to six susceptible people.[66] Those most at risk lived in the same household. The sick then transmitted to others, and the epidemic spread as long as there were enough susceptible people coming into contact with the sick. Epidemics subsided when nonsusceptible people broke up the pattern, and ended as the transmission ratio dropped toward and then below one, but before all susceptible people had been infected.

Among American Indians, however, smallpox may, if close and prolonged contact was generally more common, have spread to larger proportions of people in each of the earliest transmission cycles within a community. It may have been more difficult for anyone in the community to escape exposure. The town of Chester illustrates a general pattern of transmission in European communities, where communication of the infection outside a household depended on contacts of the necessary kind at markets and at work, in church, in visits by friends and relatives to the sick person, and in other settings, such as children visiting playmates, that brought susceptible people in close and prolonged contact with the sick.[67]

66. Hiroshi Nishiura, Stefan O. Brockmann, and Martin Eichner, "Extracting Key Information from Historical Data to Quantify the Transmission Dynamics of Smallpox," *Theor. Biol. Med. Model.*, 2008, 5, available at http://www.tbiomed.com/content/5/1/20, posit 6 to 6.9 (accessed 4 February 2010). Raymond Gani and Steve Leach, "Transmission Potential of Smallpox in Contemporary Populations," *Nature*, 2001, *414*, 748–51, point out that transmission ratios for smallpox have been estimated at as low as 1.5 and as high as 20.

67. On this pattern of transmission in the nineteenth century, when it was studied closely, see Great Britain. Royal Commission on Vaccination. *Final Report of the Royal Commission on Vaccination*, 3 vols. (London: HMSO, 1896–1897), vol. 2, Appendix 3: "Report of Dr. Sidney Coupland on the Outbreak of Small-pox in the Dewsbury Union in 1891–2," 58–60 and 142; vol. 2, Appendix 6 "Report of Dr. Sidney Coupland on the

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In Europe, where smallpox was endemic and exposure recurrent, 80–90% of people had smallpox at some point in their lives, mostly before the end of childhood. American Indian communities may have differed in that everyone, or nearly everyone, was intensively enough exposed to smallpox to fall sick in the first outbreak in the people's life experience.

Exposure among Indians rests also on transmission between settlements, a factor that some historians group under nutrition and others under social disruption.[68] Smallpox was brought to the New World from Africa and Europe, but not enough is yet known about how it was transmitted from one locale to another within the Americas. Indians traded goods, hunted, and trekked over long and short distances in the period 1500–1800. John Lawson, who walked the backcountry of the Carolinas in 1700 and 1701, found Indians, especially the men, to be restless, constantly seizing occasions to visit other settlements, including the English at Charleston.[69] The speculation is often made that Indians received smallpox in still-viable viruses in the blankets and clothing of people who had been sick, sometimes given to them by the colonizers. Much likelier is the hypothesis that already infected but not yet sick people from one community carried the disease with them in their travels. Perhaps people with mild cases continued to go about ordinary activities, including travel. In Lawson's day, European physicians were just beginning to understand the delay between exposure/transmission and the appearance of symptoms.

Transmission between locales before 1800 remains virtually terra incognita for understanding smallpox in the Americas, Africa, and Asia. Even though trade in goods and slaves may not have been as highly organized in the New World as in Europe and Africa, it is obvious that smallpox outbreaks did spread from place to place,

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Outbreak of Small-pox in the Borough of Leicester in 1892–3," 51–66; and vol. 2, Appendix 7, "Report of Dr. Sidney Coupland on the Outbreak of Small-pox in the City of Gloucester in 1895–96"; *Epidemic of Smallpox in Muncie, 1893* (Indianapolis: W.B. Burford, 1894); and J. H. L. Cumpston. *The History of Small-Pox in Australia, 1788–1908* (Melbourne: Albert J. Mullett, 1914), 12–14.

68. "Infected Indians panicked, fled to neighboring villages, and spread contagion even further." Kelton, "Avoiding the Smallpox Spirits," 46.

69. For example, see John Lawson, *A New Voyage to Carolina*, ed. Hugh Talmage Lefler (Chapel Hill: University of North Carolina Press, 1967), 20, 37.

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eventually covering vast distances.[70] Flight from outbreaks may have played an important role in the New World. Times of hunger or drought may have pushed people to migrate, exposing the hungry and thirsty to smallpox in the new locales to which they migrated and creating the conditions of smallpox exchange. However, it is also possible that smallpox was spread mainly in what seems to have been the European manner: travel by people who had been exposed and were incubating their own cases but not fleeing the sick.

It is especially transmission within settlements where American Indians can be seen to have been at a disadvantage. In communities where Indians carried out daily activities in close proximity to one another, smallpox may have been transmitted more efficiently than in any other population of that period.

Maternal antibodies and pregnant women The immune system begins to develop during gestation but does not reach full development, equivalent to the adult immune system, until about age fifteen. Different parts of the system develop in different sequences and paces from the early weeks of gestation through infancy into childhood. Newborns rely on maternal antibodies passed to them during gestation for protection against self-immunizing diseases the mother has had. Especially in the third trimester, the mother transfers immunoglobulin antibodies from her specific antibody repertoire of memory cells through the placenta to the fetus. Those neutralizing antibodies prevent or attenuate infections of specific diseases. A mother who has had smallpox transfers orthopoxvirus-specific IgG antibodies to a full-term baby in such a volume that the newborn has an antibody level equal to or greater than the mother's own level, and the capacity to resist variola and other orthopoxvirus infections.[71] That antibody level wanes during the early months of life, but may continue to have some effect for up to twelve months.[72]

70. For example, Kelton, *Epidemics and Enslavement*, 143–57.

71. C. Henry Kempe, "Studies on Smallpox and Complications of Smallpox Vaccination," *Pediatrics*, 1960, *26*, 176–89; and P. G. Holt and C. A. Jones, "The Development of the Immune System during Pregnancy and Early Life," *Allergy*, 2001, *55*, 688–97.

72. Rolf M. Zinkernagel, "Maternal Antibodies, Childhood Infections, and Autoimmune Diseases," *N. Engl. J. Med.*, 2001, *345*, 1331–35; and Hanson, *Immunology of*

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In this way, newborns are protected against many diseases until they begin to build their own complexes of memory cells from the self-immunizing diseases they have.[73] Where smallpox was endemic many mothers had had the disease and were able to transmit memory cells to their infants during gestation. In Europe, nearly all of the 80–90% of people who ever contracted smallpox did so before adulthood and before reproducing. In populations where smallpox visited periodically, as it did Iceland, some generations of mothers had memory cells from earlier in life and some did not. In smallpox naïve populations, such as in the New World, mothers were systematically unable to transmit any protection.

Evidence from eighteenth-century Europe shows that nearly all infants under three months in age were spared dying from smallpox during epidemics, that mortality remained low among those aged three to six months, and that infants of six months and older were about as likely to die as were children aged one year.[74] In the New World, infants would have received no protection from their mothers. A single source, which breaks down case fatality rates for a mild variant of smallpox, alastrim, within infancy, shows that infants under three months who had smallpox, and therefore were presumably not protected by maternal antibody, were even likelier to die than older infants in the same population.[75] That is, the case fatality rate was higher in younger than older infants. Thus extrapolating from case fatality rate averages for infants in populations where mothers had had smallpox may sharply understate the risks faced by infants unprotected by maternal immunity.

Nor would sick mothers and fathers with severe cases have been able to care for children sick at the same time. Infants were at high risk because of the absence of maternal antibody protection, and

Human Milk. See also Pearay L. Ogra, David K. Rassin, and Roberto P. Garofalo, "Human Milk," in *Infectious Diseases of the Fetus and Newborn Infant*, 6th ed., ed. Jack S. Remington et al. (Philadelphia: Elsevier Saunders, 2006), 211–43. Breastfed infants acquire some additional maternal antibodies, which seem to work against diseases of the gut and to have little effect on smallpox.

73. Holt and Jones, "Development of the Immune System."

74. For example, Haygarth, "Population and Diseases of Chester, in the Year 1774," giving age-specific mortality from smallpox.

75. Eurico Suzart de Carvalho Filho et al., "Smallpox Eradication in Brazil, 1967–69," *Bull. World Health Organ.*, 1970, *43*, 797–808.

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young children were at high risk when their parents were sick at the same time, and unable to provide water and other elements of basic care.

Women are more vulnerable to dying from smallpox when they are pregnant than at other points in life because they are likelier to develop the most severe clinical types. Pregnant women with smallpox are also subject to much higher risks of fetal death and miscarriage, premature birth, and congenital smallpox in neonates.[76] Not having had smallpox in childhood meant that all pregnant women in the indigenous population of the Americas were exposed, at each initial epidemic in their lives, to extremely high fatality rates.

Smallpox in the New World would therefore have killed many more infants in gestation, infants, and pregnant women than it did in Europe. Many in the cohort of infants alive when an epidemic began would have died. Moreover, many among the women then pregnant would also have died, removing not just the infant about to be born but all the infants that woman would later have carried to term.

None of these hypotheses gives the kind of information necessary to determine how much more lethal smallpox was to New World Indians. The best estimate that can be made extrapolates from experience in Iceland in its 1707–09 epidemic. In that epidemic newborns had maternal antibody protection only if their mothers had had smallpox in the last prior outbreak, in 1670–72; people born since that outbreak were susceptible.[77] Mortality among susceptible people was certainly higher than the 26 percent suggested as the overall proportion.[78] If Iceland's population was distributed by age

76. Julia A. McMillan, "Smallpox and Vaccinia," in *Infectious Diseases of the Fetus and Newborn*, ed. Remington et al., 927–32; Rameshwar Sharma, Ramavatar Sharma, and Davendra K. Jagdev, "Congenital Smallpox," *Scand. J. Infect. Dis.*, 1971, *3*, 245–47; Rao, *Smallpox*, 120–29; Fenner et al., *Smallpox*, 42 and 54–55; and Daniel E. Hassett, "Smallpox Infections during Pregnancy, Lessons on Pathogenesis from Nonpregnant Animal Models of Infection," *J. Reprod. Immunol.*, 2003, *60*, 13–24.

77. Steffensen, "Smallpox in Iceland."

78. There were 7,847 deaths in a segment of the population numbering 29,722, which forms the basis for Steffensen's overall estimate of mortality at 26 percent. However, that is too low because Steffensen makes no adjustment for people old enough to have had smallpox in 1670–1672.

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like that of Sweden in 1750,[79] and if 90 percent of the susceptible population got smallpox in each outbreak, then mortality could have been as high as 40 percent. Only a few infants, born to older mothers who had had smallpox in 1670–72, could have been protected by maternal antibody; most women of ages to be pregnant in 1707–09 epidemic were unprotected by prior cases.

Iceland's experience suggests that the overall fatality rate in smallpox could have been as high as 40 percent. Smallpox in the New World was more lethal still whenever there was no prior exposure and where transmission efficiency was higher than in Europe. Among American Indians overall fatality rates of 50 percent seem plausible.

CONCLUSION

Variola minor or another mildly lethal variant of smallpox was in circulation in Europe and Africa by the sixteenth century, and was probably carried to the New World. However, the catastrophic epidemics suffered in the New World were outbreaks of variola major or another highly lethal variant. To have killed the proportions of American Indian populations that reports from the period indicate, smallpox has seemed to have needed allies: aggravating factors that added to the effects of disease itself. European observers certainly thought as much; because the mortality they saw and heard about surpassed anything familiar from their own experience with this disease, they sought to identify exacerbating causes for heavy mortality in individual outbreaks. Historians have been interested in this and in the cumulative effect of smallpox over several centuries.

Some of the factors suggested as having aggravated the effects of smallpox among American Indians seem not, in the light of the research reviewed here, to have had much impact. First, except for some people with severe protein-energy malnutrition, vaccination with vaccinia virus proved safe in tests undertaken in India and Nigeria. Nutrition is not known to play a role in susceptibility to orthopoxvirus infections, and the research projects undertaken in India and Nigeria indicate that the immune response in most poorly nourished people is adequate to cope with orthopoxvirus

79. G. Sundbärg *Bevölkerungsstatistik Schwedens, 1750–1900* (repr., Stockholm: Allmänua förlaget, 1970), 82.

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infections in ways similar to what happens in such infections in well-nourished people. To make the argument that poor nutrition contributed significantly to American Indian mortality from smallpox will require new evidence.

Second, the suggestion has also been made that a specific genetic characteristic may have undermined the ability of American Indians to combat smallpox. The ABO hypothesis failed in replication, and in any case seems not to apply to American Indians. Given the intricacies in the interaction of pathogens and the host immune response, there are many other ways in which sixteenth-century American Indians could have been disadvantaged in the face of Old World diseases. However, their later tolerance of vaccination in a manner similar to people of European and African backgrounds suggests that this does not apply to orthopoxviruses. Third, Francis Black's hypothesis of genetic homogeneity among American Indians, which made them more prone to develop certain diseases once infected, may apply to measles but is unlikely to apply to smallpox.

Fourth, social disruption is a recurrent theme in European reports about smallpox epidemics in the Americas. Europeans believed that smallpox in American Indians was complicated by a lack of care and lack of food and water, even a failure to bury the dead. This idea seems plausible, within limits. For periods of up to two weeks, when it is possible that everyone in a small settlement was sick at the same time, the sick may have lacked water and food, and dehydration, but probably not starvation or malnutrition, may have complicated their sicknesses enough to cause death, especially in children. The still healthy may have fled in fear, and in that way denied care to the sick. Moreover, people staying in the community and still able to provide care may have been reluctant or unable to approach fellow residents in the pustular stage of smallpox.

Two factors added significantly to the smallpox peril for American Indians. Ordinary patterns of behavior in communities where people slept, ate, or engaged in other activities in close proximity, and where people freely visited the sick, ensured that the disease would spread quickly through a settlement and achieve something approaching universal infection in a single epidemic. Smallpox's incubation period meant that infected but not yet sick people could easily travel, or flee, to even distant settlements before falling sick and transmitting the disease. The implication is that,

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among American Indians, smallpox was often transmitted from person to person in highly efficient ways.

The most important factor in the catastrophic lethality of smallpox for American Indians was a product of the very novelty of this disease. Mothers who had not had smallpox could not pass protective antibodies to their developing infants, and they could not care for their young children when they themselves were sick. In Europe and Asia, the very young, infants up to six months, were usually protected because smallpox was endemic and their mothers had had this self-immunizing disease. In those regions parents were rarely sick at the same time as their children; they had had smallpox in childhood. In the Americas no one was safe, not in the initial epidemics, and not also in those later outbreaks that were, like the Iceland epidemics, widely enough spaced in time to mean that most people in a settlement had not previously been exposed. Moreover, women who were pregnant when infected often miscarried, or had hemorrhagic smallpox and died.

Smallpox by itself was capable of causing death among American Indians on a scale that surpassed anything familiar from Europe or Asia in individual outbreaks. Extrapolations of case fatality rates from other populations, including West Prussian cities in 1796 and India in 1974–75, significantly understate the threat that American Indians faced because young infants in Europe and Asia were usually protected by maternal antibodies, and parents were not sick alongside their children.

Smallpox's failure until about 1800 to establish an endemic presence in the Americas means that many outbreaks were spaced far enough apart for mothers and infants alike to have no immune protection. That pattern in the Americas meant episodic catastrophe in place of the heavy year-to-year toll in Europe. The European population adjusted to endemic smallpox, growing even in the presence of variola major. The population of American Indians, devastated in initial epidemics and some later ones as well, and confronting other insurmountable factors, too, suffered far more severely.

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