

What Should the Victor Do with the Vanquished? Deciding the Fate of Smallpox

by

Justin A. Pruneski

Department of Biological and Environmental Sciences
Heidelberg University, Tiffin, OH

Part I – The Decision

In December of 1979, the Global Commission for Certification of Smallpox Eradication officially confirmed, for the first time in history, the eradication of an infectious disease. The World Health Organization (WHO) had purposefully ended the transmission of a pathogen and completely removed the disease from the human population. This was no simple feat and this was no ordinary disease. Smallpox, arguably the worst infectious disease mankind has known, had been ripping through the world's population for thousands of years, leaving hundreds of millions of corpses in its wake and many more victims horribly disfigured or blind. It is estimated to have killed around 300 million people in the 20th century alone, and immediately before its eradication, smallpox was killing approximately two million people each year. Thanks to a worldwide vaccination campaign, there has not been a single case of smallpox in humans since 1978.

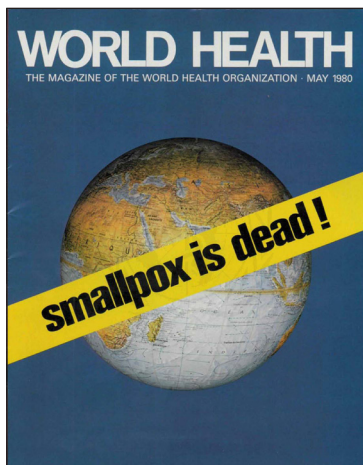


Figure 1. Cover of WHO magazine *World Health* from May 1980 announcing the eradication of smallpox.

While smallpox has been eradicated, the variola virus, the pathogen that causes the scourge, is not extinct; there are still viable strains that have the potential to infect humans and re-enter the population. Frozen stocks of the virus are being held in maximum containment laboratories at the Centers for Disease Control (CDC) in Atlanta, Georgia and in the State Research Center of Virology and Biotechnology (VECTOR) in Koltsovo, Russia. In the decades following the eradication, WHO officials, world leaders, and scientists have strongly debated whether the stocks should be destroyed, and whether that would deal a final deathblow to the disease once and for all.

Questions

1. What would you do if it were your decision; would you vote to retain or destroy the stocks?
2. What would you need to know to make a more informed decision?

Part II – Know Your Enemy

History's Scourge

Smallpox entered the human population from an unknown animal host, periodically infecting small nomadic tribes and then rapidly burning itself out as it ran out of susceptible hosts. Around 5,000–8,000 years ago, at the dawn of agriculture and civilization when humans were starting to form settlements large enough to support the sustained spread of the virus, smallpox started to take hold and became endemic in many human populations. Slowly, the virus began to mutate and change enough to diverge from its former host to become a strictly human pathogen. As people traveled to new lands, the virus went with them and spread into new territories, quickly infecting indigenous populations that had no previous exposure or immunity.

Smallpox was described in Sanskrit medical texts from as early as 1500 BC and has been implicated in numerous events that have changed the course of human history. The name *variola* was given around 580 AD by Bishop Marius of Avenches in Switzerland as a form of the Latin word *varius* (spotted) or *varus* (pimple). The disease eventually became known as “smallpox” to distinguish it from syphilis, which, at the time, was known as the “great pox.” In 430 BC, smallpox may have been responsible for the Plague of Athens, which killed a third of the population and led to the defeat of Athens by Sparta in the Peloponnesian war. The disease decimated Alexander the Great’s army in 327 BC on his march to India and accelerated the fall of the Roman Empire when Marcus Aurelius succumbed in 180 AD.

Spanish explorers carried variola virus with them to the New World, which allowed them to conquer the natives. When the Aztecs saw their people ravaged by the disease while the European explorers remained unaffected, they saw it as a sign from god that Cortez should be allowed to enter and rule. Approximately 90% of the native population of the Massachusetts Bay area was killed by smallpox after the arrival of the pilgrims. In perhaps one of the first acts of biological warfare, during the 1760s the English deliberately infected Native Americans with blankets contaminated with pus from smallpox victims. Overall, it is estimated that there were over 72 million natives in North and South America when Columbus landed in 1492, but only 600,000 remained in 1800 as a result of the warfare and disease that settlers had brought.

The disease struck commoners and royalty alike; famous victims include Pharaoh Ramses V of Egypt (1160 BC), Roman Emperor Marcus Aurelius (180), Pocahontas (1617), Queen Mary II of England (1694), King Louis II of Spain (1724), Tsar Peter II of Russia (1730), Queen Eleanora of Sweden (1741), and King Louis XV of France (1774). Other famous figures survived their bout with smallpox, including George Washington, Andrew Jackson, Abraham Lincoln, Joseph Stalin, Mozart, and Beethoven.

Smallpox is thought to have killed more humans than any other infectious disease, including the Black Death of the Middle Ages, with estimates as high as 300 million people in the twentieth century alone. British historian Thomas Babington Macaulay described some of the horrors of the disease: “the smallpox was always present, filling the churchyards with corpses, tormenting with constant fear all whom it had not yet stricken, leaving on those whose lives it spared the hideous traces of its power, turning the babe into a changeling at which the mother shuddered, and making the eyes and cheeks of a betrothed maiden objects of horror to the lover” (*The History of England from the Accession of James II*, Claxton, Remsen, & Haffelfinger, Philadelphia, 1800).

Question

3. Describe at least three ways that an infectious disease, like smallpox, can significantly impact history.

Etiology

Smallpox is caused by two variants of an enveloped virus with a double-stranded DNA genome from the genus *Orthopoxvirus* and family *Poxviridae*. Variola minor virus causes a less severe form of the disease, known as alastrim, while variola major virus causes the most prevalent and severe form of smallpox. The large brick-shaped virus (325nm × 250nm) consists of an outer protein shell, surrounded by an envelope, with an inner dumbbell-shaped core that

contains genetic material (Figure 2). The viral genome has ~187,000 base pairs of double-stranded DNA containing 200 genes, both of which are of substantial size for a virus. The virus usually enters human hosts through infecting cells of the respiratory tract where it travels to cells of the blood and lymphatic system, begins replicating, and eventually spreads to the skin.

The incubation period of the disease is twelve days on average before signs and symptoms appear. It starts with fever, headaches, and backaches often accompanied by vomiting. Vesicles appear first in the mouth and throat and then quickly spread to the face, forearms, hands, legs and feet. The higher density on these areas compared to the trunk is a characteristic of smallpox called a “centrifugal rash” (Figure 3). The vesicles slowly become opaque and pus-filled, with a slight dimple in the center, before they crust over after about two weeks. Different forms of the rash can occur based on individual response to the virus. A discrete rash is one in which the pustules remain distinct and separate from each other, while a confluent rash occurs when pustules combine to raise large sections of skin from the underlying tissues. The hemorrhagic form of the disease, also known as “black pox,” causes blood to pool under the skin and in other locations in the body. In some patients, the pathogen can initiate a cytokine storm, which means the host immune system is triggered to become hyperactive causing massive tissue damage.

Death usually comes 10–16 days after onset of symptoms. Overall, smallpox killed roughly one third of its victims (~30% mortality rate), but the rate was much higher in children, and the confluent and hemorrhagic forms were nearly always fatal. Before the 19th century, the disease was so prevalent that people were almost always exposed as children and either succumbed to the disease or survived and gained lifelong immunity. Those who survived were often left with disfiguring facial scars and many were partially or completely blind. Even in the middle of the 20th century, there were no truly effective treatments of smallpox. The disease had to run its course, while patients received supportive care: fluid replacement, pain medication, or, more recently, antibiotics to treat secondary bacterial infections. Patients were often kept at home to be treated by immune family members rather than risk spread to other patients in a hospital.

Smallpox was a human disease; there were no other animal hosts for the virus and humans were the only known reservoir. The variola virus was transmitted from human to human through direct or indirect contact, either through prolonged close contact with a patient experiencing the rash, or through contaminated clothing or bedding. There were no asymptomatic carriers of the virus that could spread the disease without ever experiencing symptoms. Infected individuals could shed the variola virus into the air during coughs and sneezes or onto clothing or bedding through oozing from pustules. Estimates of how quickly the disease spread, termed the multiplier of disease, varied considerably, but an infected person would, on average, infect a dozen other people.

Question

4. Why was variola virus such a dangerous pathogen?

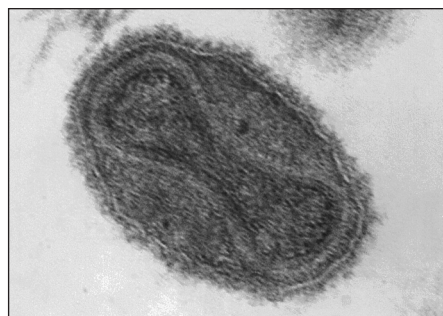


Figure 2. Electron micrograph image of the variola virus. Credit: Centers for Disease Control and Prevention's Public Health Image Library (PHIL), with identification number #1849.



Figure 3. Smallpox victim showing the centrifugal rash. Credit: “The Diagnosis of Smallpox,” Ricketts, T. F. Casell and Company, 1908 Plate XXIV.

A Long and Hard-Fought Victory

As early as 1000 BC, it was observed that pockmarked survivors of smallpox never contracted the disease again. This led to the first known practice of inoculation, called variolation, in which a scab or pus from smallpox patients with a mild form of the disease, was purposefully introduced into healthy individuals. This practice originated in India and China, but spread and became prevalent in certain areas of the world, despite the associated risk. The method attempted to create a mild infection of smallpox in order to induce lifelong immunity, but since people were being infected with actively replicating variola virus, they could develop and die from smallpox, and they could spread the disease to others, causing new outbreaks.

Variolation remained the primary means to stem the scourge until the late 18th century, when Edward Jenner, an English country doctor discovered a safer alternative. He and others observed that milkmaids could develop cowpox, which produced sores on cow's udders and a few bluish pustules on milkers' hands, but they did not seem to catch smallpox. He used experiments to test the hypothesis that contracting cowpox can protect an individual from getting smallpox. He started by variolating thirteen adults who had never had smallpox, but had cowpox or a related disease horsepox. None of the thirteen developed the characteristic inoculation site rash (Figure 4), suggesting they were already immune to smallpox. On May 14, 1796, Jenner made two half-inch incisions into the arms of an 8-year-old boy named James Phipps and inserted pus and lymph from a cowpox pustule. One month later, he inoculated the boy with pus from a case of smallpox and the child did not develop the disease. This type of experiment, known as a challenge trial, would be considered highly unethical today. Many were still skeptical, so Jenner successfully repeated the experiment with several more children, including his 11-month-old son Robert. Jenner coined the term "vaccine" and "vaccination" to describe this practice, from the Latin word *vacca* for "cow." His work was published and his approach quickly spread throughout England and to the U.S. where it replaced variolation.

The scientific basis for why Jenner's vaccine worked came much later with advancements in the understanding of the immune system. Patients who had recovered from smallpox were unlikely to get the disease again because their immune system developed memory that protected the individual from subsequent infections with variola virus. When given the live virus vaccine that infects the individual with cowpox virus, the immune system responds to the virus and produces memory that can also protect against smallpox due to similarities between the two viruses. By inoculating people with cowpox virus from the pus of cowpox lesions or from the inoculation site of someone recently vaccinated (Figure 4), immunity to smallpox could be induced in a relatively safe way. In 1932, it was discovered that the virus strain used to make the smallpox vaccine was no longer cowpox virus but rather a new virus, which was named vaccinia, that is distinct from both the cowpox and variola viruses. How and when vaccinia virus replaced cowpox virus is not fully understood, but it has subsequently been used as the basis of the live smallpox vaccine and as a model system for orthopoxvirus research.

Through a series of developments, the vaccine was able to be produced on a large scale and was made into a stable freeze-dried form that could travel well and remain viable for long periods of time. Multi-dose vials of vaccine could be resuspended at the point of use and quickly given to hundreds of people at an extremely cost-effective, one penny

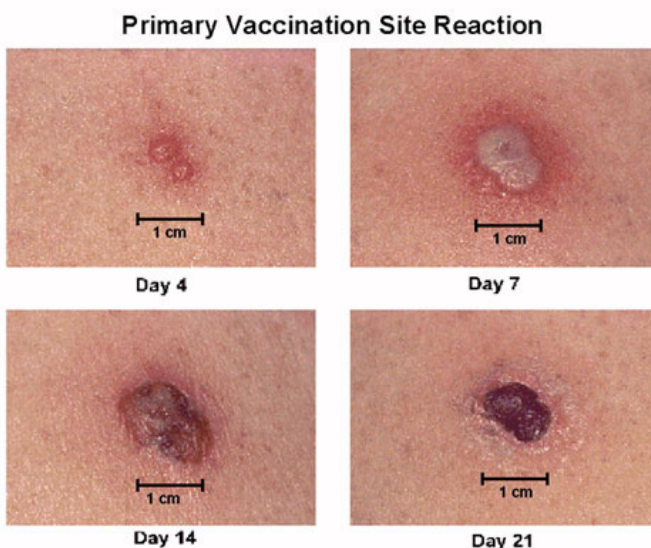


Figure 4. Characteristic localized rash that develops at the site of inoculation. A permanent scar remains as a mark of those who have been vaccinated. Credit: CDC, <<https://emergency.cdc.gov/agent/smallpox/vaccination/facts.asp>>.

per dose. It was administered using a metal needle with two prongs (bifurcated) that could be easily sterilized, dipped into the liquid vaccine and then inserted multiple times into the arm to trigger an immune reaction (Figure 5). Blister formation and the subsequent vaccination site scar gave an easy visual cue that the immunization worked (Figure 4).

While the vaccine was aimed at preventing the disease, it could also be given up to 4–5 days after exposure to the virus and still offer some protection or reduce the severity of the disease. Because a replicating virus was used, it elicited a strong immune response and gave long-lasting immunity, but exposure to the vaccine was not without risks. When the disease was devastating the world, the risks were deemed acceptable, but it is estimated that 1 in 5 people today might not be able to safely receive the live virus vaccine due to risk of complications or even death. Those at risk include children under 1 year old, pregnant women, individuals with eczema or HIV, those with immune disorders or on immunosuppressive drugs, and cancer patients taking chemotherapy. Anyone with these at-risk individuals in their home might also not receive the vaccine due to the risk of spreading the virus.

Question

- How did developments in the prevention of smallpox help lead to our current practice of immunization?

Countdown to Zero

With incremental improvements to the vaccine and mass vaccination programs, smallpox was largely eliminated in many developed nations including the U.S. in the early 20th century. Even though the disease still raged in developing nations, this gave many the idea and hope that it might be possible to eradicate the disease. Edward Jenner himself knew that, even without a way to treat smallpox, the vaccine could be used to end the disease by depriving the virus of susceptible hosts: “It now becomes too manifest to admit of controversy, that the annihilation of the Small Pox, the most dreadful scourge of the human species, must be the final result of this practice” (*The Origin of the Vaccine Inoculation*, D.N. Shury, London, 1801).

After a false start that began in 1958, the World Health Organization formed the Intensified Smallpox Eradication Programme in 1966, headed by D.A. Henderson, a global effort to rid the disease from the over thirty countries where the virus was still endemic. The goal was to eradicate the disease in ten years by vaccinating 80% of people in affected nations to generate herd immunity. When mass vaccination proved infeasible, an alternative strategy of surveillance and containment was enacted in which outbreaks were quickly identified and individuals in the affected area and surrounding regions were given the vaccine to create a protective ring of immunity around the outbreak. Groups of relatively unskilled workers, coordinated by Henderson and WHO, went from village to village educating people, checking vaccination records, and hunting down new smallpox cases (Figure 6). This strategy was extremely effective and eliminated the disease in country after country.



Figure 5. A multi-dose vial of freeze-dried vaccinia and the bifurcated needle used to inoculate it into a patient's arm. Credit: James Gathany/CDC, PD.



Figure 6. Posters offering rewards for information about potential smallpox cases helped the eradicators track down the last cases of the disease. Credit: WHO/René Gauch.

Finally, in October 1977, just past the ten-year goal, the last natural case of smallpox in the world occurred and was contained in Somalia. After another two and a half years of intense surveillance and verification, the eradication was made official in 1979.

The eradication effort utilized hundreds of thousands of workers from over 70 countries. The eradicators received resources and vaccines from a number of supporting countries led by the U.S. and Russia, with an estimated total cost of \$112 million. This high price was an investment that paid off handsomely, as it is estimated that the eradication has saved \$1 billion annually on making or purchasing vaccines, vaccination programs, surveillance, outbreak response, and treatment of smallpox patients or complications from vaccines. Before eradication, smallpox was killing 2 million people each year, so the eradication effort has likely saved 50–75 million lives. In his popular nonfiction book on smallpox, *The Demon in the Freezer*, Richard Preston highlighted the scope and significance of the eradication of the disease:

“That we have never seen [a smallpox infection] in our lives was an extraordinary thing, a gift, unasked for, unexpected, and now unnoticed. A handful of doctors had given it to us, joined by thousands of village health workers. They had forged themselves into an army of peace. With a weapon in their hands, a needle with two points, they had searched the corners of the earth for the virus, opening every door and lifting every scrap of cloth. They would not rest, they would not stand aside, and they gave all they had until variola was gone. No greater deed was ever done in medicine, and no better thing ever came from the human spirit.” (Random House, NY, 2002)

Questions

6. Why was smallpox a good candidate for eradication?
7. What were the challenges to eradication?

Part III – The Demon in the Freezer

Immediately after variola virus was eliminated from human populations, and indeed, even during the eradication efforts, the discussion began on what to do with the stocks of variola virus held in labs around the world. In 1975, there were approximately 75 known labs that held frozen stocks of variola virus. After a lab accident in U.K in 1978 in which two people were infected and one died from variola virus that was inadvertently released from a research lab, the World Health Organization began an effort to formally ask labs to destroy stocks or send them to two designated sites in the U.S. (Atlanta, Georgia) or Russia (Moscow). This effort resulted in the destruction or consolidation of all known variola virus stocks into the two official repositories, but there was little oversight or regulation of the process. After the consolidation was completed in 1983, WHO officials met periodically to decide the fate of variola virus. Although the votes were very close at times, and sometimes even in favor of destroying the stocks, the virus was continually given a stay of execution.

The major consideration in the debate centers around whether variola virus could re-enter the human population and from what source. The frozen stocks and research using the variola virus represent a risk that the virus could be released from the lab or be compromised by terrorist activity. It is also widely believed that clandestine (secret, unaccounted for) stocks could exist outside of the two official repositories. In 1992, a Russian scientist Ken Alibek defected to the United States and revealed a secret biological warfare program that was weaponizing and stockpiling variola virus and other infectious agents during the 1970s and 80s. The fate of these viral stocks is not known and many fear other countries such as Afghanistan, Iran, Iraq, or North Korea might have obtained the virus during the chaos that ensued during the fall of the Soviet Union. Independent of nations purposefully holding samples of the virus, variola virus stock vials, unaccounted for during the consolidation, have been discovered in laboratory freezers periodically and as recently as 2014. Similarly, scabs from smallpox victims have been found in century old envelopes and books, and the bodies of victims exist throughout the world. While the virus is generally not stable in these forms, the possibility exists of finding some ultra preserved specimen or body containing viable virus. In this modern era of genomics, biotechnology, and synthetic biology, the virus could potentially be re-created from published sequence data and current DNA synthesis methods. There also remains the concern that a smallpox-like disease may emerge through evolution of monkeypox virus or another related animal virus. Since the eradication of smallpox, humans have lost most of the cross-protection that the vaccinia vaccine afforded, increasing the incidence of monkeypox, and turned it into an emerging threat.

Retentionists, those in favor of keeping the stocks, argue that the possibility of the virus re-entering the population from other sources outweighs the risk of the frozen stocks being compromised. They still see smallpox as a very real threat to a population that is largely susceptible; no U.S. civilian born after 1972 was vaccinated, and even those that received the vaccine will likely have little protection decades later. They argue the stocks are needed to learn more about the virus and disease to help mitigate the effects of a re-emergence. They believe more basic research needs to be done on the pathogenesis of the virus and more applied research to develop better diagnostic tools, antiviral drugs, and vaccines. They worry that the virus could be genetically engineered to be resistant to current antivirals or vaccines, which has already been done for a related mousepox virus. There is also the philosophical and ethical concern that humans should not purposefully cause an organism to go extinct. An additional consideration is, with some of the growing tensions between the U.S. and Russia, neither side may completely trust each other enough to destroy their stocks.

Destructionists, those in favor of sterilizing the stocks, argue that they represent the most likely source of variola virus re-emergence, either through a lab accident or terrorist activity. Destroying the stocks would mitigate that risk and send a message to the rest of the world. Head of the eradication effort, D.A. Henderson stated: “What we need to do



Figure 7. Cryogenic vials containing stocks of a virus can be preserved indefinitely by flash freezing and storage in liquid nitrogen. Credit: Margaret Shirra.

is create a climate where smallpox is considered too morally reprehensible to be used as a weapon... It would make the possession of smallpox in a laboratory a crime against humanity” (Quoted in Preston, Douglas. *The Demon in the Freezer*. Random House, NY, 2002). Destructionists argue that research on pathogenesis, vaccines, and antivirals has already accomplished its major goals and further research is not worth the risks. Research on smallpox could still continue using related viruses or the sequenced genomes and individual variola virus proteins that can be made in the lab. Since the vaccine is based on vaccinia not variola virus, they argue that having the stocks of live virus will do little to help if smallpox does re-emerge. The U.S. has stockpiled enough vaccines for all of its citizens that can help contain any potential future outbreaks, but other countries may not be so prepared.

Question

8. In light of the new information, do you think the frozen stocks of variola virus should be retained or destroyed? What argument most compelled you and why?

Part IV – Will Other Diseases Go the Way of Smallpox?

Based on the success against smallpox, other infectious diseases have been, or are currently being considered candidates for eradication. Each of the diseases below has features that might make eradication possible, but also many challenges to eradication:

- Cysticercosis
- Guinea Worm Disease (Dracunculiasis)
- Hookworm Infection
- Lymphatic Filariasis
- Malaria
- Measles
- Mumps
- Poliomyelitis (Polio)
- Rinderpest (Cattle Plague)
- Rubella (German Measles)
- Yaws
- Yellow Fever

Questions

9. For this question you will be assigned one of these twelve diseases. For your disease, research the pathogen that causes the disease and the eradication efforts to answer the following questions:
 - a. What is the nature of the disease? (Pathogen, type of organism, mode of transmission, signs and symptoms, etc.)
 - b. What makes this disease a potential candidate for eradication?
 - c. What are the challenges to eradication of this disease?
 - d. What progress has been made towards eradication?
10. If you could eradicate one other infectious disease not on this list, what would it be and why? Why might that disease not be considered a candidate for eradication at this time?

