Smallpox Vaccine: The Good, the Bad, and the Ugly

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ABSTRACT

Smallpox inarguably shaped the course of human history by killing countless millions in both the Old World and the New World. Dr. Edward Jenner's discovery of vaccination in the late 18th century, and the global eradication of smallpox in the 1970s, rank among the greatest achievements in human history. Amidst recent growing concerns about bioterrorism, smallpox vaccination has resurfaced from the history books to become a topic of major importance. Inoculation with vaccinia virus is highly effective for the prevention of smallpox infection, but it is associated with several known side effects that range from mild and self-limited to severe and life-threatening. As the United States moves forward with plans to vaccinate selected health care workers and the military, and perhaps offer the vaccination to all citizens in the future, it is important to fully understand and appreciate the history, risks, and benefits of smallpox vaccination.

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HISTORY OF SMALLPOX VACCINATION AND GLOBAL ERADICATION

Smallpox has been a scourge against humanity for at least the past 1500 years, and perhaps much longer than that. There is no mention of the disease in ancient Greek writings, but plagues of pustular disease in the Roman Empire bore a strong resemblance to smallpox. The literary record suggests that smallpox became established in the Mediterranean by the third century AD, and it was described in China around the same time.[1] Smallpox subsequently changed the course of history and killed millions of people in both the New World and the Old World.

Smallpox is caused by the variola virus, a DNA virus of the genus *Orthopoxvirus*. Humans are the only known reservoir for this virus. It is transmitted from person to person, and natural infection occurs by inhalation of respiratory droplets or contact with infected material on mucous membranes. Historical data suggest that smallpox is not highly transmissible, and high population densities are required to sustain transmission. Persons who have close, prolonged contact with an infected patient are at highest risk.[2] After a 10 to 14 day incubation period, the infected person develops severe symptoms with fever, malaise and headache.[3] A maculopapular rash then develops with involvement of the face, mucous membranes, trunk and extremities. The lesions become pustular and deep over the subsequent 1 to 2 days, with scab formation by day 10. Patients are most infectious during the first week of the rash when viral shedding is greatest from ulcerated lesions in the oral mucosa. The overall mortality rate is about 30%, with most deaths occurring during the second week of illness.

The earliest smallpox prevention efforts date back to at least the 10th century in China, when physicians found that nasal inoculation of susceptible persons with material from smallpox lesions would sometimes provide immunity.[4] The practice of inoculation appears to have arisen independently in several other regions prior to the 17th century, including Africa and India, but the practice did not gain popularity in western Europe until the 18th century. The wife of an English ambassador, Lady Montagu, observed inoculation in Turkey, and later had her own child successfully inoculated during a smallpox epidemic in England.[5] In this procedure a lancet or needle was used to deliver a subcutaneous dose of smallpox material to a susceptible person. The procedure, also known as variolation, was controversial. It generated immunity in many cases, but it also killed some people and contributed to smallpox outbreaks.

A more safe and effective method for smallpox control originated in the late 18th century when Dr. Edward Jenner of Gloucestershire, England noticed that milkmaids exposed to cowpox appeared to be immune to smallpox. He tested his hypothesis by inoculating a boy with cowpox pus and subsequently challenging him with smallpox. The experiment was a success, and Jenner prepared a paper describing this case along with 13 other individuals who had contracted either horsepox or cowpox before being exposed to smallpox. In one of the worst editorial decisions of all time, the Royal Society rejected the paper and suggested that Jenner cease his cowpox investigations.[5] Jenner wisely ignored this advice, named the cowpox material the "vaccine virus", and thus discovered the concept of vaccination.[1, 6] Early smallpox vaccinations utilized pustular material from one vaccinated person to directly inoculate another person by scratching the material into the recipient's arm. Later improvements included the inoculation of cow flanks to obtain larger quantities of virus, and use of glycerol solution as a preservative.[7] A textbook published in the early 20th century described the vaccination process as follows:

> A spot, usually on the upper arm, is scraped by a lancet, so that the outer layers of the epidermis are removed; the spot is then rubbed with an ivory point, quill or tube, carrying the virus. A slight and usually unimportant illness or indisposition follows, and the arm is sore for a time, a characteristic scar remaining.[8]

The modern vaccine was conceived in the 1950s when a technique was developed to produce a heat-stable, freeze-dried vaccine. This process used centrifugation to create a suspension of virus, which was then freeze-dried in ampules. This had the advantage of allowing long-term storage without refrigeration.

The first large smallpox eradication effort was launched in 1950 with the goal of eliminating smallpox in the Americas. In 1958, the World Health Assembly passed a resolution calling for the global eradication of smallpox. Although some countries established smallpox eradication programs, there was no coordinated infrastructure. Many programs faltered due to insufficient vaccine supplies and limited resources.

The more virulent form of smallpox, variola major, was widespread in the United States during the 19th century, but only two major outbreaks occurred from 1900 to 1925.[9] In contrast, the milder form of smallpox (variola minor) was common until the 1930s. After 1949, there were no endemic cases of smallpox in the United States, but the disease continued to be a serious problem in less developed countries. By 1966, smallpox remained endemic in 33 countries.[7] After extensive debate, the World Health Assembly approved $2.4 million to initiate a global eradication program over the next 10 years. Early in the campaign the Soviet Union and the United States donated more than 150 million doses of vaccine. Around the same time, the bifurcated needle was developed, which simplified delivery and reduced the volume of vaccine required.

The global eradication effort, led by D.A. Henderson, originally used a strategy of mass vaccination campaigns to achieve 80% vaccine coverage in each country. This goal proved difficult to attain in many underdeveloped countries, but a serendipitous discovery led to a more effective strategy. Insufficient vaccine supplies in Nigeria led Dr. William Foege to try a strategy of aggressive case-finding, followed by vaccination of all known and possible contacts to seal off the outbreak from the rest of the population.[5] This was the first time such a strategy was employed during the global smallpox eradication campaign, although it was also used in Leicester, England in the late 19th century.[9] This strategy, known as surveillance-containment or ring vaccination, led to the disappearance of smallpox in eastern Nigeria even though the population coverage was less than 50%. The relative benefits of ring vaccination versus mass vaccination have been debated, but epidemiological evidence from Africa and Asia suggests that both lower population density and higher population vaccine coverage contributed to the elimination of transmission in many regions.[10]

The last naturally-acquired case of the variola major was identified in Bangladesh in late 1975. The last case of illness caused by the less virulent strain (variola minor) occurred in Somalia in 1977.[5,11] The World Health Assembly declared that smallpox had been eradicated from the earth in 1980. Although the significance of this event may be under appreciated, it stands as one of the greatest accomplishments of the 20th century, if not one of the greatest human accomplishments of all time. Several factors unique to smallpox contributed to the success of this effort, including easily-diagnosed clinical disease, lack of subclinical infections, absence of transmission during prodrome, and lack of an animal reservoir.[12]

In 1976, the World Health Organization requested that all laboratories with smallpox virus either destroy the virus or submit their stocks to one of two collaborating centers in the United States (Centers for Disease Control) or the Soviet

Union (Moscow Institute). Most laboratories complied, but there is evidence that smallpox was subsequently developed as a biological weapon in the Soviet Union.[6] Large volumes of weaponized smallpox virus may be unaccounted for, and there is concern that smallpox stocks may have been acquired by other nations. There have also been allegations that Russia has developed recombinant strains of smallpox with increased virulence and infectivity.[3] These concerns have contributed to the current interest in renewed smallpox vaccinations, particularly since the September 11, 2001 terrorist attack and the use of anthrax as a biological weapon later in 2001.

SMALLPOX VACCINE

The most widely used virus for smallpox inoculation has been vaccinia, which belongs to the genus *Orthopoxvirus* along with variola virus. Other species of *Orthopoxvirus* include cowpox (the virus used by Jenner), monkeypox, and camelpox, among others. Vaccinia is a double-stranded DNA virus with a wide host range. Its origin is uncertain, and there are many strains of vaccinia with different biological properties.[9] Vaccinia induces both cellular and humoral immunity to variola virus.[13] The current U.S. licensed smallpox vaccine (Dryvax, Wyeth Laboratories, Inc.) was prepared from calf lymph using the New York City Board of Health (NYCBOH) strain of vaccinia. Production of this vaccine was discontinued in 1982. The National Pharmaceutical Stockpile also includes the Aventis Pasteur vaccine, which was also manufactured from calf lymph. Multiple other strains of vaccinia have been used in other regions the world.

Long-term research is underway using recombinant DNA technology to develop a safer vaccine that will provide an effective immune response without replication of vaccinia virus.[14] Two companies are currently funded by the United States government to develop and test a vaccine based on the modified Ankara strain of vaccinia, which is nonreplicating in mammalian cells (Washington Post, February 26, 2003). In the short term, two new, unlicensed smallpox vaccines have been developed by Acambis/Baxter Pharmaceuticals. Both use the NYCBOH strain of vaccinia virus, but one is cultured from human embryonic lung cell culture and the other uses African green monkey (vero) cells.[15] At this time it is not known if these vaccines will be more or less reactogenic than the current calf-lymph derived vaccine. Clinical trials are underway. Until a new vaccine is licensed by the U.S. Food and Drug Administration, existing doses of Dryvax can be diluted 1:10 and still generate an adequate immune response if the number of required vaccinations exceeds the number of doses in the national stockpile.[16]

Effective smallpox vaccines have a vaccinia titer of approximately 10^8 pock-forming units per mL, and more than 95% of individuals develop a 'take' with neutralizing antibodies after primary vaccination.[13] The efficacy of the vaccine has not been evaluated in controlled studies, but epidemiologic data suggest that a high level of protection persists for up to 5 years after vaccination, with partial immunity persisting for 10 years or more.[11] The vaccine will prevent infection or reduce the severity of illness if given within a few days following exposure to smallpox.[3]

Smallpox vaccine is administered by puncturing the skin multiple times with a bifurcated needle containing a small quantity of vaccine. A small papule develops after 3 to 5 days, following the virus replication in the dermis. The papule evolves into a vesicular and pustular stage over 8 to 10 days.[17] There is typically an indurated area surrounding the central lesion. This is followed by scab formation with development of a residual scar. The process of vesiculation and pustule formation defines a 'take' of the vaccine. The take is considered equivocal if a pustule, ulcer, or scab, does not develop at the vaccine site; revaccination is recommended in this situation.[17] Skin reactions following revaccination tend to be milder and have an accelerated course.

ADVERSE EFFECTS OF VACCINATION

Frequency and Clinical Features

Smallpox vaccine is less safe than other vaccines routinely used today. The vaccine is associated with known adverse effects that range from mild to severe. Mild vaccine reactions include formation of satellite lesions, fever, muscle aches, regional lymphadenopathy, fatigue, headache, nausea, rashes, and soreness at the vaccination site.[13,18,19] A recent clinical trial reported that more than one-third of vaccine recipients missed days of work or school because of these mild vaccine-related symptoms.[18]

In the 1960s, serious adverse events associated with smallpox vaccination in the United States included death (1/million vaccinations), progressive vaccinia (1.5/million vaccinations), eczema vaccinatum (39/million vaccinations), postvaccinial encephalitis (12/million vaccinations), and generalized vaccinia (241/million vaccinations).[20] Adverse events were approximately ten times more common among those vaccinated for the first time compared to revaccinees.[20] Fatality rates were also four times higher for primary vaccinees compared to revaccinees.[21]

Inadvertent inoculation is the most common adverse event associated with smallpox vaccination. It occurred at a rate of 529 per million vaccinations in a 1968 study.[20] Inadvertent or accidental inoculation usually occurs when a person transfers the vaccinia virus from the vaccination site to another location on their body, usually the eyes, mouth, nose, or genitalia.[20,22] Most lesions resolve without therapy, but vaccinia immune globulin (VIG) may be useful for difficult lesions. VIG can be considered for use in patients with severe ocular vaccinia, but it may increase the risk of corneal scarring.[17,23]

Progressive vaccinia (a.k.a. vaccinia necrosum, vaccinia gangrenosum) is defined as an uncontrolled replication of vaccinia virus at the vaccination site that leads to a slow and progressive necrosis of surrounding tissue.[24] Satellite necrotic lesions typically develop, and ultimately vaccinia

virus may be found in other tissues and organs.[24] This condition typically affects individuals with incompetent immune systems.[24,25] The cardinal clinical signs of progressive vaccinia include an unhealed vaccination site >15 days post vaccination, and the lack of inflammation or an immune response at the vaccination site.[24,25] Untreated progressive vaccinia is fatal, but treatment with VIG or the antiviral cidofovir may be effective in some cases.[24,25] VIG and thiosemicarbazone treatment in the late 1960s and 1970s reduced the fatality rate for progressive vaccinia from near 100% to 33%.[23,25,26] Surgical debridement or amputation may also provide some benefit.[24, 25]

Eczema vaccinatum is a cutaneous dissemination of vaccinia virus that usually occurs in persons with pre-existing skin disease. It is typically mild and self-limited, but it may be severe or fatal, especially in young children. Death is usually caused by extensive viral dissemination, fluid and electrolyte imbalance, and bacterial sepsis.[25,27] Treatment with VIG or antivirals may be effective in some cases.[25] Supportive care used for burn victims may help retain proper fluid and electrolyte balance and reduce mortality from eczema vaccinatum.[2] Improvements in intensive care therapy during the 1960s likely contributed to the lowering of the fatality rate for eczema vaccinatum from 10% to 1% to 2%.[26,27]

Post-vaccinial encephalitis is a rare adverse event that frequently leads to death, especially in infants and young children. Reported case fatality rates range from 9% to 40%.[25,28] Ten to twenty-five percent of surviving patients have permanent neurologic sequelae.[25,28] No predisposing conditions have been identified for this condition, and treatment with VIG has little to no effect.[21,23,25]

Generalized vaccinia results from blood-borne dissemination of vaccinia virus.[23,25] Patients affected with this condition have a generalized rash that is typically self-limited and requires no therapy. VIG can be administered to speed recovery.[23,25] This condition may occur in immunosuppressed individuals, but it can also affect those without any underlying illness or risk factors.[25]

Risk factors

Persons with atopic dermatitis or eczema, irrespective of disease severity or activity, are at risk of developing eczema vaccinatum and should not receive pre-exposure smallpox vaccination.[15] Additionally, persons with skin conditions that disrupt the epidermis, such as burns, seborrheic dermatitis, psoriasis and severe acne, are at risk of complications and should not be vaccinated until their skin lesions resolve.[15] Vaccination is also contraindicated in individuals who have the inherited skin condition Darier's disease (keratosis follicularis).[15]

Persons with incompetent immune systems are at risk of complications following smallpox vaccination. This group includes persons who are immunocompromised due to a specific illness (e.g. HIV/AIDS, leukemia, lymphoma, inherited immunodeficiency), organ transplant recipients, and those taking immunosuppressive medications such as high-dose corticosteroids or methotrexate.[15] Vaccination is also contraindicated for people who have severe autoimmune diseases such as systemic lupus erythematosus that may impair the immune system.[15] Additionally, persons receiving either radiation therapy or chemotherapy are at risk of complications and should not be vaccinated. Infants less than one year of age should not be vaccinated because several studies have demonstrated that they are at increased risk of death and other complications.[15,23,27] Pregnant women should not receive pre-exposure vaccination because vaccinia virus can be transmitted to the fetus resulting in a rare, but serious, complication called fetal vaccinia.[15,20] Additionally, people with allergies to vaccine components, or those with a history of a serious prior reaction to smallpox vaccination, should not be vaccinated.[15]

Transmission to Contacts

Vaccinia virus may be spread from person-to-person, which means that people who have close contact with recent vaccinees may be exposed to the virus and may be at risk of developing complications. For this reason, pre-exposure smallpox vaccination is contraindicated in persons who have close contact with individuals who have some of the risk factors described above.[15] In particular, close contacts of persons with a history of eczema or atopic dermatitis, or contacts of immunocompromised individuals should not be vaccinated. Individuals should not be vaccinated if they have close contact with pregnant women or infants. Close contacts include both household members and sexual partners.

Eczema vaccinatum and inadvertent inoculation are the most frequently reported conditions in contacts of recent vaccinees. Twenty percent of the eczema vaccinatum and inadvertent inoculation cases reported in a 1968 study occurred in contacts of vaccinees.[21] In this study and several others from the 1960s, eczema vaccinatum was more severe in contacts than in those who were vaccinated themselves.[21,27] No cases of progressive vaccinia or postvaccinial encephalitis have been documented in contacts of vaccinees.[29,30]

Most cases of contact vaccinia occur through direct person-to-person transfer of virus.[30] Frequent hand washing and proper maintenance of an occlusive dressing over the vaccination site may reduce the likelihood of viral transmission.[30] Aerosol transmission of vaccinia virus from a vaccinee to a contact has never been definitively documented.[30] Nosocomial and fomite transmission of vaccinia are rare, but have been reported.[22,30]

ACIP RECOMMENDATIONS FOR PRE-EVENT VACCINATION

The Advisory Committee on Immunization Practices (ACIP) began serious discussions about the risks and benefits of pre-event smallpox vaccination in 2001. At that time, the committee concluded that the risks of vaccination outweighed the benefits in the current pre-event setting except for a very small number of individuals.[11] The ACIP revisited this issue in June 2002 in light of the September 11, 2001

attacks, but continued to recommend against vaccination of the general population in the current pre-event setting of no confirmed smallpox. However, the ACIP did recommend vaccination for the following groups: persons pre-designated by the appropriate public health authorities to conduct investigation and follow-up of cases; and selected personnel in facilities pre-designated to serve as referral centers to provide care for the initial cases of smallpox.

The ACIP then changed its recommendation again after further discussions with state health agencies and bioterrorism experts. In October 2002, the group stated that suspected smallpox patients are likely to present to hospitals and facilities that provide their usual care, rather than the pre-designated smallpox response facilities. Recommendations published in February 2003 state that each acute care hospital should identify a group of health care workers who can be vaccinated and trained to provide care for the first suspected smallpox cases.[31] These hospital-based teams would provide care 24 hours per day for at least 2 days until additional health care providers are vaccinated. The ACIP recommendations also state that previously vaccinated health care workers should be vaccinated whenever possible to decrease the risk of vaccine complications. The current ACIP guidelines provide detailed and useful recommendations regarding the composition of smallpox health care teams, vaccination procedures, prevention of contact transmission and contraindications to pre-event vaccination.[31]

The concept of limited pre-event vaccination is supported by a recently published policy model that evaluated the impact of different smallpox attack scenarios. The models suggest that pre-event vaccination of health care workers will yield a net reduction in fatalities unless the risk of an attack is very low.[32] The model simulated several different attack scenarios, including a building attack (350 infected) and a high-impact airport attack (100,000 infected). If the model assumptions are valid, pre-event vaccination of health care workers would save lives if the probability of attack is greater than .22 for the building attack and .002 for the high-impact airport attack.

VACCINATION OF THE GENERAL PUBLIC

The federal government has indicated that voluntary vaccination of the general public may be approved after health care workers and first responders have been vaccinated. Increasing the number of vaccinated persons will inevitably lead to increases in morbidity and mortality due to vaccinia, and current evidence suggests net harm would result if smallpox vaccine were made available to the general public on a voluntary basis.[32] Such a policy would pose a risk to both the vaccinees and their close contacts (who presumably have not consented to vaccinia exposure) with little or no benefit under many attack scenarios. If this complex public health decision is delegated to individual citizens, some individuals will be unable to weigh the risks and benefits for true informed consent.[2] If real cases of smallpox ever occur in the United States, the risk-benefit assessment of mass vaccination may favor mass vaccination, and federal and state agencies are preparing for this possibility.

The title of this article refers to the good, bad and ugly of smallpox vaccine. We have attempted to show that the vaccine is a critical tool for controlling smallpox ("the good"), despite a relatively higher risk of complications in some individuals ("the bad"). The "ugly" refers not to the vaccine, but to the potential reintroduction of smallpox more than 20 years after its eradication. We hope that our great-grandchildren will be oblivious to this concern after many years have passed without the reemergence of this deadly disease.

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