The Role of Vaccines in Controlling Smallpox

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ABSTRACT

Since smallpox killed millions of people in both the Old and New Worlds, it undoubtedly influenced the path of human history. Two of the greatest accomplishments in human history are the discovery of vaccination by Dr. Edward Jenner in the late 18th century and the worldwide eradication of smallpox in the 1970s. Smallpox, caused by the variola virus, was one of the most devastating infectious diseases in human history before its eradication in 1980 through a global vaccination campaign led by the World Health Organization. This review explores the clinical presentation, diagnostic advancements, vaccination strategies, and public health initiatives associated with smallpox. Clinical evaluation relied heavily on identifying characteristic symptoms such as a centrifugal rash and febrile prodrome, with modern diagnostic methods, including polymerase chain reaction (PCR), offering rapid and accurate confirmation. Vaccination played a pivotal role, with live replicating vaccines like ACAM2000 providing robust immunity but presenting safety concerns, especially in vulnerable populations. Safer alternatives, such as the non-replicating JYNNEOS vaccine, have been developed to address these issues. The eradication effort, marked by innovative strategies like mass and ring vaccination, remains a blueprint for combating infectious diseases. Despite its eradication, smallpox research remains relevant due to concerns about bioterrorism and the re-emergence of related orthopoxviruses like monkeypox. Future efforts should focus on advancing vaccine safety, improving diagnostic infrastructure, and developing antiviral therapies to ensure preparedness for emerging threats. This legacy underscores the enduring importance of scientific innovation and global collaboration in achieving and maintaining public health milestones.

Key words: Poxvirus, vaccination, immunization, variola**,** smallpox

INTRODUTION

An extremely infectious and often deadly virus. Additionally, the condition is referred to by the Latin names "Variola" and "Variola vera," which are derived from the Latin words "varus," which means "pimple," or "various," which means "spotted." First used in Europe in the 15th century, the term "smallpox" was used to differentiate "Variola" from "great pox" (syphilis).It is believed that between 300 and 500 million people died from smallpox in the 20th century. [5] Supposedly, it started in Africa and spread to China and India. Smallpox is a dangerous illness brought on by a virus. It spreads easily from person to person and causes fever, tiredness, and a rash with blisters all over the body. This disease was very deadly in the past, killing many people. [30] Those who survived often had scars from the blisters. Its symptoms included fever, severe skin lesions, and systemic complications, leading to significant morbidity and mortality. Before the advent of vaccination, smallpox outbreaks decimated populations, caused social disruption, and altered the trajectory of history. Vaccination transformed smallpox from a global public health scourge to the first human disease eradicated by deliberate effort. This monumental achievement highlighted the transformative role of vaccines and served as a foundational success story for modern immunology and public health campaigns. [1] Variola major, the most dangerous type of smallpox, had a death rate of almost 30%. Variola minor, a less harmful type of disease produced by a distinct strain of variola, was discovered during the eradication campaign to have a fatality rate of roughly 1%.[5] Monkeypox patients may have a similar condition, albeit with fewer systemic symptoms. Nevertheless, mortality from monkeypox was as high as 10% to 17% in some sections of the Congo River basin throughout the 1970s and 1980s. [3] The Variola virus belongs to the Poxviridae family. The biggest and most intricate viruses that infect humans are pythons. Human illness is caused by several poxviruses, such as monkeypox, vaccinia (the smallpox vaccine virus), and molluscum contagiosum. [2] Before a prairie dog-related outbreak in the USA connected to rodent imports from Africa, monkeypox, a zoonotic disease resembling smallpox, was only seen in equatorial Africa. [4] While some of the other poxviruses can cause localized illness in humans, the majority are only found in particular animal hosts. [18]

Figure 1. Smallpox

Figure 2. Smallpox vaccine

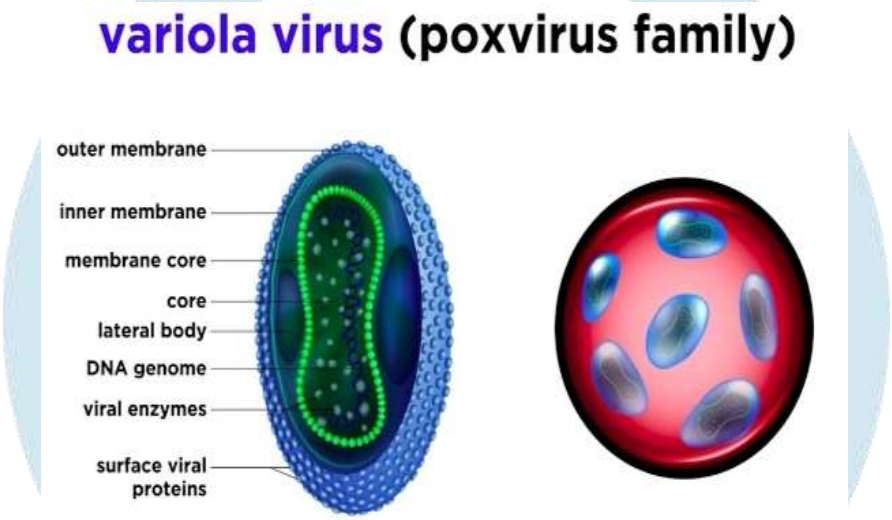

Figure 3. Variola virus. [5]

History of smallpox and vaccination

The Variola virus causes smallpox, one of the oldest and most devastating diseases in human history, with evidence indicating its existence for over 3,000 years.[5] Ancient Egyptian mummies, such as Pharaoh Ramses V (circa 1157 BCE), show signs consistent with smallpox, indicating its presence in early civilizations.[6] The disease likely originated in northeastern Africa or the Indian subcontinent, as early agricultural societies provided conditions for its emergence.[7] Historical Chinese records from 1122 BCE describe symptoms resembling smallpox, and texts from ancient India also document its effects, demonstrating its recognition as a significant health problem.[8] Smallpox spread widely through trade and warfare, becoming a global epidemic over centuries. Its introduction to the Americas by European colonizers in the 15th and 16th centuries caused devastating outbreaks among indigenous populations, who had no prior immunity. Mortality rates reached as high as 90% in some communities. [9] Efforts to control smallpox began in 10th-century China with variolation, a method involving deliberate exposure to smallpox material to induce immunity. This practice spread to the Ottoman Empire and, by the 18th century, to Europe, where it became a standard method for controlling outbreaks. However, variolation carried significant risks, including severe infection and death.[10] The turning point came in 1796 when Edward Jenner, an English physician, discovered that exposure to cowpox, a related virus, conferred immunity to smallpox. He tested his hypothesis by inoculating James Phipps, an eight-year-old boy, with cowpox material and later exposing him to smallpox, which he did not contract. This marked the advent of vaccination, derived from *vacca* (Latin for cow), and laid the foundation for modern immunology. [11] By the mid 20th century, smallpox remained endemic in many countries. In 1967, the World Health Organisation (WHO) launched the Intensified Smallpox Eradication Program, focusing on mass vaccination campaigns and "ring vaccination" strategies to contain outbreaks. [5] Through these efforts, the last natural case of smallpox was reported in Somalia in 1977. In 1980, the WHO declared smallpox eradicated, marking the first and only human disease to be eliminated through vaccination. [5, 12]

Period	Event
Ancient Times	Evidence of smallpox-like rashes found on mummies in Egypt (1570–1085 BCE).
1000s CE	Earliest recorded use of variolation (an early smallpox inoculation method) in China.
16th–18th Centuries	Smallpox spreads through Europe, Africa, and the Americas, causing high death rates.
1796	Edward Jenner develops the first smallpox vaccine using cowpox, starting modern vaccination.
1800s	Smallpox vaccination has become more widespread in Europe and America.
1959	WHO begins a global campaign to eradicate smallpox, but with limited initial success.
1967	WHO intensifies eradication efforts, focusing on mass vaccinations and containment strategies.
1980	WHO officially declares smallpox eradicated worldwide.

Table 1. History of smallpox Period and event

SMALLPOX ERADICATION

At the beginning of the 19th century, arm-to-arm vaccinations were common, but by the end of the century, vaccines made from live animals' hides by extracting lymph were taking their place. Calves were the main subject of this, but donkeys and horses were also employed. This approach increased the potential risk of transmissible spongiform encephalopathies and complicated matters by posing a risk of contamination from bacteria, fungi, and other viruses, even if it made it possible to transfer manufacturing capacity even to remote places.[13] A century of unstandard and unregulated smallpox vaccination led to considerable regional variations in vaccine storage and administration practices as well as vaccine strains. [5] In 1965, the World Health Organisation (WHO) required that 1×10^{-8} plaque-forming units per milliliter be present in the undiluted smallpox vaccine.[14] Several techniques were used to inject the vaccine into the epidermis, but due to its usefulness, the bifurcated needle was adopted as the standard vaccination technique in 1968. To facilitate the transfer of the vaccination to the skin, the bifurcated needle was made to hold roughly 2.5 mL of vaccine suspension. The flat prongs also ensured that the vaccine was consistently delivered to the proper depth during the several shallow punctures that were performed.[5, 15] Certain vaccinia virus strains were more frequently utilized for vaccination during the smallpox eradication effort. American vaccines were derived from the New York City Board of Health (NYCBH) strain, which was created in 1856 from an English seed virus. Using chick embryos and rabbit testes, Dr. Rivers passed the NYCBH strain in the 1930s to create two attenuated strains of the virus, CVI-78 and CVII. It was questioned if either strain could provide adequate protection against smallpox, but when given as vaccinations, they both exhibited less local and systemic reactogenicity than the NYCBH strain. The Union of Soviet Socialist Republics' EM-63 vaccine strain was thought to have originated from the NYCBH strain. The WHO received a vaccine made from the EM-63 strain in the late 1960s. The Temple of Heaven (Tian Tan) strain was used to vaccinate against smallpox in China. The Lister strain was first used for vaccination in the United Kingdom in 1892, and during the Intensified Smallpox Eradication Programme, it eventually emerged as the strain most frequently used to produce smallpox vaccine. [5, 15]

Some derivatives and the parent strain	Comments
NYCBH Rivers Wyeth (Dryvax) APSV	1. NYCBH was spread among several labs and adopted different names. 2. Different passage methods led to variations in strains.
Lister (Elstree) L-IVP LC16m8 Lancy-Vaxina	1. The variola virus was thought to be the source of lister. 2. By 1971, Lister was being used by most vaccine manufacturers.
Copenhagen NYVAC	1. The pathogenicity of the Copenhagen strain was high. 2. Intentional deletion of virulence genes attenuates NYVAC.
Temple of Heaven (Tian Tan)	1. Supposed to be caused by the variola virus 2. Mainly utilised in China
Ankara MVA	The following are suggested applications for MVA: (1) immunising the general public and boosting with traditional live vaccine if necessary; (2) immunising individuals who are ineligible for traditional vaccinations; (3) immunising laboratory personnel against unintentional exposure to recombinant vaccines; and (4) immunising individuals at risk for monkeypox.

Table 2. Common strains of the vaccinia virus used in vaccinations. [15, 16,17]

Pathophysiology

The majority of knowledge regarding the pathophysiology of smallpox is derived from animal models using non-variola orthopoxviruses. [5, 19, 18] Animal research and epidemiological data have demonstrated that variola typically enters the body through the respiratory system. Infections of the skin, conjunctiva, and transplant are uncommon. The respiratory tract mucosa is initially infected, although there are no symptoms or noticeable lesions. The virus replicates in the respiratory epithelium before entering the reticuloendothelial system and being absorbed by macrophages, most likely following a brief primary viremia. [5,18] In the reticuloendothelial system, asymptomatic replication persists until a severe secondary viremia occurs, which triggers the onset of symptoms. [5,18] There is a window of opportunity for immunization following exposure [5, 20, 18] and potentially for antiviral prophylaxis due to the interval between infection and secondary viremia. [21] In the common form of smallpox, this secondary viremia is transient. The virus can be found in the blood till death in hemorrhagic instances. High levels of virus are produced in the respiratory secretions, and the initial focal lesions appear in the oropharynx just before the rash starting (Figure 4). At the onset of the rash, respiratory virus shedding and, consequently, infectivity are at their peak. [22, 18] When macrophages enter the epidermis and cause necrosis and edema, skin lesions develop. When polymorphonuclear cells enter, vesicles develop and eventually turn pustular. These tumors, as well as the bone marrow, spleen, liver, kidneys, and other organs, can harbor viruses. Toxaemia, which is defined by coagulopathy, hypotension, and multiorgan failure, was typically blamed for smallpox mortality. [23,18] Although the precise causes of mortality are unclear, inflammatory mediators [24] and direct cytopathic effects of viruses might play a part. Although bacterial superinfections were frequent, their role in there doesn't seem to be much mortality. [24, 18] Although it is hard to determine how much, modern supportive care may reduce mortality. In the fight against smallpox, innate, humoral, and cellular immunity all appear to play a significant role. Before eradication, research on humoral immunity revealed that antibodies that neutralize, complement-fixation, and haemagglutination-inhibit were detected two to three weeks after infection. Patients with hemorrhagic illness had reduced or undetectable antibody concentrations. Most patients experienced a decline in complement-fixation antibodies within a year of infection, and within five years, haemagglutination-inhibiting antibodies dropped to low levels. Neutralizing antibodies can last a lifetime and are detectable for decades after infection. It's still unknown what these titers mean clinically. Data on the cellular immune response from the pre-eradication era are scarce. [18,25] Understanding different orthopoxviruses indicates that cytotoxic T lymphocytes play a critical role in preventing the infection from spreading too quickly. [26] The most serious side effect of vaccination is progressive vaccinia, which occurs in people with T-cell deficiencies. [27] The lower mortality following remote immunization may be explained by memory T cells, which survive for at least 50 years following vaccination. [28, 18]

Flow chart Pathophysiology

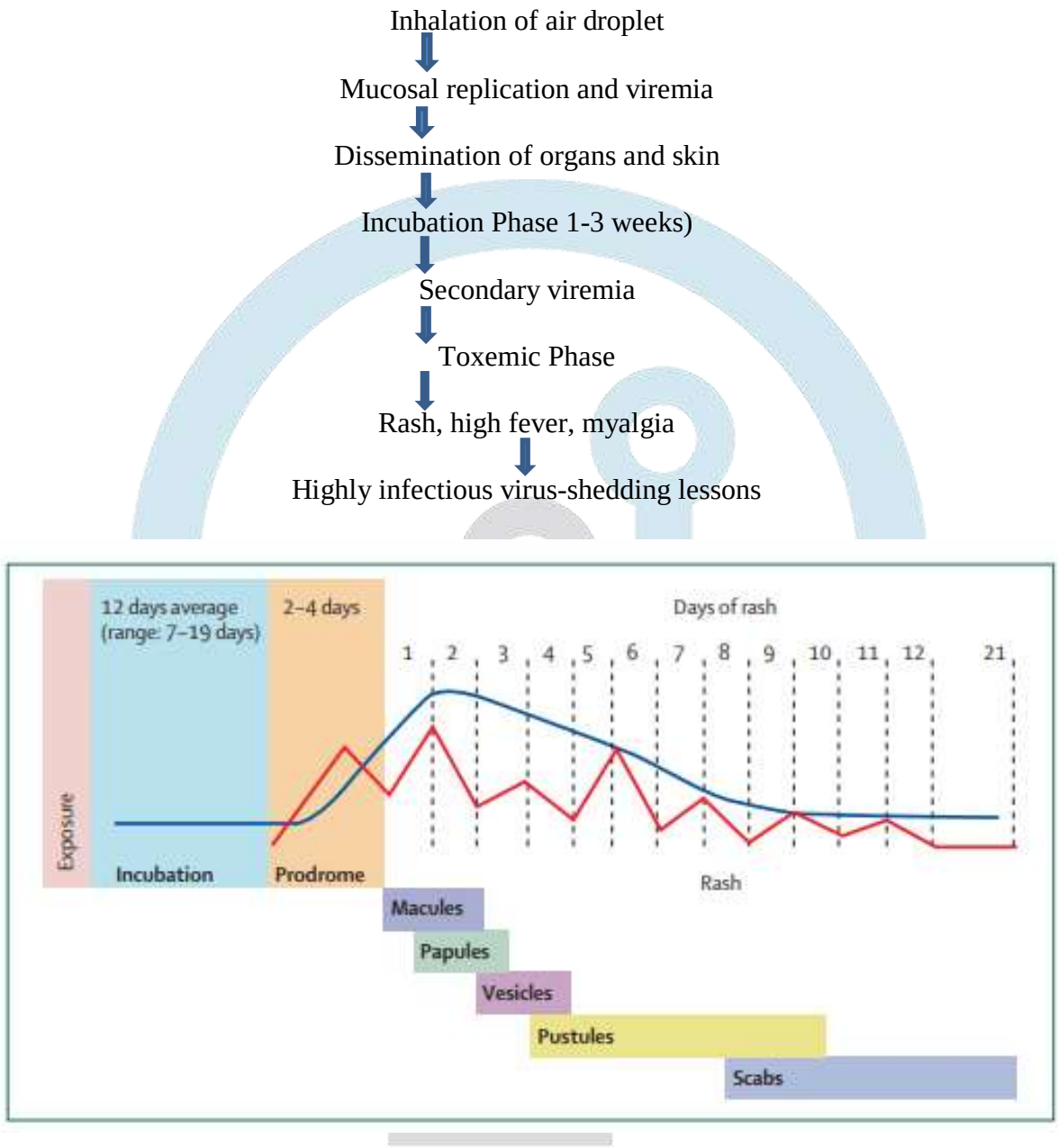

Figure 4. Stages smallpox: fever, rash formation, and viral shedding Blue line indicates respiratory virus shedding, while the red line indicates temperature. [18]

Types of smallpox

1. Ordinary Smallpox

Represented the majority of cases (89–90%) in unvaccinated individuals. Initial symptoms included a high fever, severe malaise, headache, and back pain (prodromal phase). A characteristic rash appeared, progressing from macules to papules, vesicles, pustules, and then scabs. The rash followed a centrifugal distribution most dense on the face, arms, and legs, with fewer lesions on the trunk. Approximately 30% in severe cases. Survivors often had lifelong pitted scars (pockmarks). [29,31]

2. **Modified Smallpox**

It occurred primarily in previously vaccinated individuals. A milder disease course with fewer and more superficial lesions. The prodromal phase was shorter or less pronounced, and recovery was quicker. Extremely low, as the immunity provided by vaccination greatly mitigated the severity of the disease. [30, 31]

3. **Malignant (flat) Smallpox**

A rare but severe form, accounting for 5-10% of smallpox cases. Lesions remained soft, flat, and velvety, failing to develop into raised pustules. The skin often appeared dark and dusky due to toxemia, and there was no clear demarcation of lesions. Systemic symptoms were severe, including prolonged high fever and widespread organ damage. Very high (up to 95%), especially in children. [29, 31]

4. Hemorrhagic Smallpox

A rare and highly lethal form, more common in pregnant women. Severe toxemia with extensive internal and external bleeding (petechiae, purpura). Skin lesions are often hemorrhaged, leading to a "black pox" appearance. Patients usually succumbed rapidly, often before the characteristic rash fully developed. Almost 100%, due to widespread hemorrhage and hock. [29, 31]

5. **Variola sine eruptions (smallpox without rash)**

A rare manifestation is seen mostly in vaccinated individuals or those with partial immunity. Patients experienced fever and systemic symptoms similar to smallpox but without the appearance of the characteristic rash. Often detected in close contact with smallpox patients during outbreaks. Mild and typically resolved without complications, as partial immunity limited disease progression. [30, 31]

Sr. no	Type of Smallpox	Characteristics	Case death rate
1.	Ordinary	• Most popular form. • 90% of cases in non-vaccinated people	30%
2.	Modified	• Milder type • Caused fewer, smaller, and more superficial lesions • Affected 2% of unvaccinated individuals; 25% of vaccinated individuals	Modified smallpox rarely resulted in death.
3.	Malignant or flat	• The lesions were smoother, developed more gradually, and consolidated. • 7% of incidents involving unvaccinated individuals	97%
4.	Hemorrhagic	• Less than 3% of cases • Difficult to identify • Rash with skin and mucous membrane hemorrhage	Near 100%
5.	Variola sine eruption (without rash)	• Infected newborns with maternal antibodies or contacts who had previously received vaccinations • Those who were impacted either showed no symptoms at all or experienced brief fever, headache, and influenza-like symptoms. • Variola sine eruption had not been shown to transmit clinical smallpox.	Not available, although less than 1% of people died from variola mild.

Table 3. Types of smallpox. [5, 31]

How do vaccines work?

How vaccination works, which is particularly relevant to the eradication of smallpox. Here's the process explained step-by-step:

1. **Weakened Virus Injected**: In a smallpox vaccination, a weakened or inactive virus similar to the smallpox virus (often the vaccinia virus, which is related but less harmful) is injected into the body. This virus is altered so that it can't cause disease but is still similar enough to the actual smallpox virus for

the immune system to recognize it. By injecting this harmless version, the immune system gets exposed to the virus without the person becoming sick. This introduction prepares the immune system to recognize and fight the real virus if it encounters it in the future.

2. **Activation of the Immune System**: Once the weakened virus is in the body, it triggers the immune system. White blood cells recognize the virus as a foreign invader and respond by producing antibodies specifically designed to target and neutralize it.
3. **Antibody Production and Memory**: The immune system stores a "memory" of the pathogen. Antibodies and memory cells specific to the smallpox-related virus are created and remain in the body for a long time.
4. **Future Protection**: If the person is exposed to the actual smallpox virus in the future, the immune system quickly recognizes it. The antibodies and memory cells produced earlier neutralize the virus before it can cause illness, providing immunity.[34]

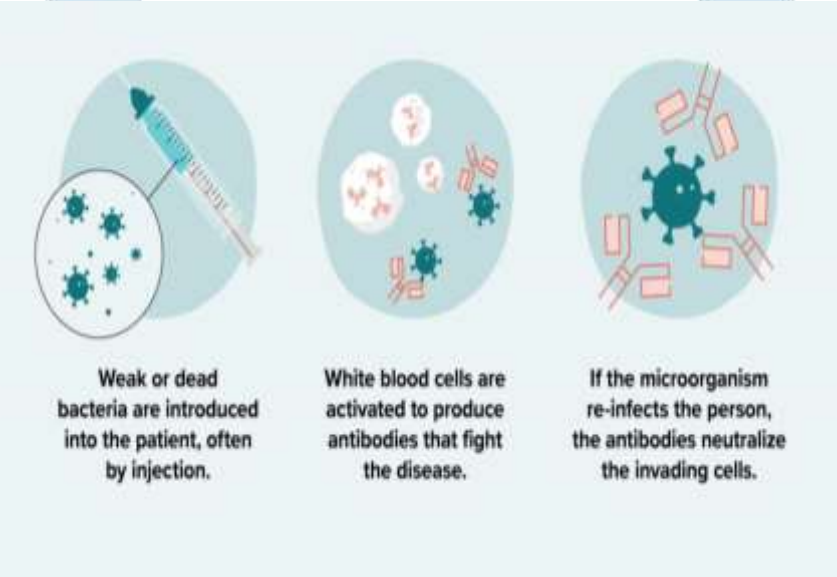

Figure 2. How the vaccine works. [34]

Biological Weapon: Smallpox

One of the most dangerous bioterrorism dangers is smallpox. When American Indians were given blankets contaminated with smallpox by British soldiers during the French and Indian War (1754–1767), it was employed as a biological weapon. Variola was created by the Soviet Union as an aerosol biological weapon in the 1980s, and tonnes of virus-laden material were produced there each year for use in intercontinental ballistic missiles.

The use of smallpox as a biological weapon raises several concerns:

1. Variola can spread from one individual to another.
2. The illness does not now have a licensed or generally accessible treatment.
3. Its death rate is high.
4. The world's population is particularly susceptible to smallpox since the United States stopped routinely vaccinating against it in 1972 and all other nations did the same by 1983. The majority of people on the planet have either never received a vaccination or received one so long ago that their immunity to smallpox has diminished.
5. Variola has a low infectious dosage and is a reasonably stable aerosol.

Because there are no symptoms at the time of exposure, a covert release of variola may not be detected until sick people begin showing up at doctor's offices and hospitals. [33, 35]

Transmission

People can contract smallpox by direct contact with bodily fluids or respiratory droplets. The virus can also be spread by contaminated bedding or clothing. The virus is not known to be carried by or transmitted to humans by insects or animals. Smallpox takes 7–17 days to incubate. [33]

1. **Airborneroute:**

- Then person-to-person
- Hospital contact
- Coughing patients
- touching of an infectious person

2. **Infectious Materials:**

- Saliva
- Vesicular fluid
- Scabs
- Urine
- Conjunctival fluid
- Possibly blood

Infection Control Measures

To stop the disease from spreading, people who have been diagnosed with smallpox or are suspected of having it should be kept apart. Patients who have smallpox or are suspected of having it should have their households and other in-person contacts vaccinated and monitored.

All hospital staff should be vaccinated, and hospital staff should follow the CDC's isolation precautions guidelines when handling smallpox patients. [5, 33]

Illness

Laboratory testing confirms the smallpox diagnosis, which is based on the patient's clinical presentation of symptoms. The symptoms, which include a high temperature, acute malaise, and tiredness with headache and backache, usually start 12 to 14 days after infection. Before spreading to the body's trunk and legs, including the palms and soles, a rash of tiny, pink pimples first emerges in the mouth, on the cheeks, and on the wrists. Within a day or two, the rash turns from fluid-filled to pus-filled. Round, deep, and hard the lesions start to crust over on days eight or nine. It is believed that a person with smallpox can spread the disease from the between when the rash first occurs and when it goes away (around two weeks). Smallpox complications include pneumonia, sepsis, arthritis, keratitis, encephalitis, and bacterial superinfections of the skin and organs. Chickenpox, the disease that is most frequently confused with smallpox, is characterized by a milder prodromal illness and rash that:

- Is more superficial
- Usually begins on the trunk and spreads centripetally.
- Lesions in different stages of evolution
- Seldom appears on the palms or soles.

Variola major and Variola minor are two closely related strains that produce smallpox. Except polymerase chain reaction (PCR) testing, the two viruses are identical. Alastrim, also known as Variola mild infection, results in fewer deaths, less severe rash, less scarring, and fewer systemic symptoms. [5,33] A number of variola main disease variants were identified at the time when smallpox was a naturally occurring illness. Refer to Table 3.

Vaccine Administration

Smallpox vaccines are administered primarily using two methods: bifurcated needle administration and jet gun injection**.**

1. Bifurcated Needle Method

- **Technique**:
  - A bifurcated needle (a forked metal needle) is dipped into the vaccine solution, which retains a small dose of the vaccine between its prongs.
  - The needle is then used to make multiple superficial punctures (typically 15) into the skin of the upper arm. This action ensures the vaccine penetrates the epidermis.
- **Advantages**:
  - Minimal vaccine waste: The needle delivers a precise dose of the vaccine.
  - Cost-effective: The bifurcated needles are inexpensive, reusable (with proper sterilization), and easy to transport.
- **Drawbacks**:
  - Slower administration compared to jet injectors.
  - Requires trained personnel to administer properly. [30, 33]

2. Jet Gun Injector

- **Technique**:
  - The jet injector uses high-pressure streams of liquid vaccine to penetrate the skin without a needle.
  - It delivers the vaccine intradermally, subcutaneously, or intramuscularly, depending on the injector's settings.
- **Advantages**:
  - Speed: Jet injectors are much faster and suitable for mass vaccination campaigns.
  - No needles: Reduces the risk of needle-stick injuries and cross-contamination.
- **Drawbacks**:
  - Higher cost: The equipment is more expensive and requires maintenance.
  - Risk of contamination: In earlier models, there was a risk of blood-borne pathogen transmission if the injector wasn't properly sterilized between uses. [30, 36]

Figure 5. Bifurcated needle

Figure 6. Jet gun

Types of vaccines used in smallpox

1. ACAM2000: Live, replicating vaccinia virus vaccine. Approved for immunization against smallpox. Used for individuals at high risk, including military personnel and laboratory workers. Delivered via a bifurcated needle using the percutaneous method. Can cause a robust immune response but requires careful handling to prevent autoinoculation or virus spread. Contraindicated for immunocompromised individuals, pregnant women, or those with eczema. [36]

2. JYNNEOS (Imvamune or Imvanex): Non-replicating modified vaccinia Ankara (MVA) virus vaccine. It is licensed to prevent monkeypox and smallpox. Suitable for people with compromised immune systems, eczema, or pregnancy. Subcutaneous injection in a two-dose regimen, spaced 28 days apart. Safer than traditional live-replicating vaccines due to their non-replicating nature. Commonly used in populations at risk of monkeypox outbreaks. [36]

3. Aventis Pasteur Smallpox Vaccine (APSV): Live, replicating vaccinia virus vaccine. An investigational vaccine stockpile, reserved for emergency use under FDA authorization. Similar to ACAM2000, typically with a bifurcated needle. Used as part of emergency preparedness for bioterrorism scenarios. Comparable efficacy to ACAM2000 but with less routine use due to its investigational status. [36]

4. Cowpox Vaccine: The first vaccine developed using the cowpox virus (historically by Edward Jenner). Historical use for smallpox prevention was replaced by more refined vaccinia-based vaccines. Lay the foundation for modern smallpox vaccination and immunology. [30]

5. **Vaccinia Vaccine**: General category, including vaccines derived from the vaccinia virus. ACAM2000 and APSV are modern vaccine-based vaccines. Integral to smallpox eradication efforts. Variations are now used for smallpox and monkeypox prevention. [30]

Sr. no	Vaccine	Type	Indications	Safety
1.	ACAM2000	Live, replicating	Smallpox, high-risk individuals	Requires careful handling; contraindicated for certain groups
2.	JYNNEOS	Non-replicating MVA	Smallpox, monkeypox	Safer for immunocompromised individuals, eczema, and pregnancy
3.	Aventis Pasteur Smallpox Vaccine	Live, replicating	Emergency use only	Similar to ACAM2000 but investigational
4.	Cowpox Vaccine	Historical	Historical smallpox prevention	Pioneered vaccination
5.	Vaccinia Vaccine	Live (varies)	Smallpox, monkeypox	Varies depending on vaccine type

Table 4. Types of vaccines used in smallpox

Symptoms and Signs

1. Variola major: Variola major has a prodrome of fever, headache, backache, and severe malaise that lasts for two to three days after an incubation period of 10 to 12 days (range 7 to 17 days). Severe stomach pain and vomiting might occasionally happen. Following the prodrome, maculopapular lesions appear on the arms, face, and oropharyngeal mucosa. They quickly spread to the trunk and legs. Oropharyngeal lesions ulcerate rapidly. The cutaneous sores became vesicular and then pustular after a day or two. The face and extremities have a higher density of pustules than the trunk, and the palms may also have them. The pustules seem firmly implanted and are spherical and tight. In contrast to chickenpox, smallpox skin lesions are common on a single body part

and occur at the same stage of development. The pustules start to crust after eight or nine days. Usually, there is severe residual scarring.

Approximately 30% of cases result in death. Death usually happens in the second week of illness and is caused by a large inflammatory response that causes shock and multiple organ failure. Hemorrhagic or malignant (flat) variants occur in 5–10% of patients with variola major. A shorter, more severe prodrome precedes generalized erythema and cutaneous and mucosal hemorrhage in the less common hemorrhagic type. Within five or six days, it is consistently lethal. A comparable, severe prodrome precedes the development of confluent, flat, nonpustular skin lesions in the malignant variant. The epidermis of survivors often desquamates. [38]

2. Variola minor: Similar but far more severe symptoms, including a less widespread rash, are caused by Variola mild. Less than 1% of cases result in death. [38]

Few more symptoms

- High fever.
- Headache.
- Body pain.
- Vomiting (sometimes).
- Rashes
- Muscle pain
- Diarrhoea
- Joint pain
- Multiple organ inflammation
- The first symptoms of smallpox usually appear 12 to 14 days after you're infected.

Clinical Evaluation for Smallpox

1. **Physical Examination and Medical History**: Diagnosis begins with a thorough physical exam and detailed medical history. Clinicians look for characteristic smallpox symptoms, such as a severe febrile prodrome, rash with lesions in the same stage of development, and a distribution pattern involving extremities and the face. Identifying these clinical signs is critical, as the disease can mimic other conditions like chickenpox or other febrile illnesses. [37]

2. **Laboratory Tests**

    - **Virus Isolation**: In specialized laboratories, smallpox viruses can be isolated using cell cultures. This method confirms the presence of the variola virus in samples such as skin lesions or fluids.
    - **PCR (polymerase chain reaction)**: PCR is a rapid and highly sensitive test to detect viral DNA, making it the gold standard for smallpox confirmation.
    - **Electron Microscopy**: Direct visualization of orthopoxvirus particles via electron microscopy provides another diagnostic tool, though less commonly used than PCR. [38]

3. **Imaging Studies**: For suspected complications, such as pulmonary involvement in disseminated infections, imaging studies like chest X-rays may be employed. This helps assess secondary effects or opportunistic infections but is not a primary diagnostic method. [37]

Discussion

The study of smallpox continues to provide invaluable insights into the fields of virology, immunology, and global health systems. Although the disease was declared eradicated in 1980, its historical impact, coupled with concerns about bioterrorism and the emergence of related orthopoxviruses such as monkeypox, ensures its relevance in medical research and public health preparedness. The clinical presentation of smallpox, characterized by fever and a centrifugal rash, remains a critical aspect of historical diagnosis. However, with modern advancements, laboratory-based diagnostics have enhanced the ability to detect and confirm variola virus infections. [38] Polymerase chain reaction (PCR) is now considered the gold standard due to its specificity and speed, allowing for rapid detection of viral DNA even in low concentrations. Virus isolation and electron

microscopy, though highly specific, are resource-intensive and confined to high-containment facilities. These methods underscore the importance of robust diagnostic infrastructure in handling potential orthopoxvirus outbreaks. Vaccination was central to the global eradication of smallpox. [33] Traditional live replicating vaccines, such as ACAM2000, were highly effective but associated with significant side effects, particularly in immunocompromised individuals or those with dermatological conditions like eczema. In contrast, newer vaccines like JYNNEOS, derived from the modified vaccinia Ankara (MVA) strain, offer a safer alternative, particularly for vulnerable populations. This shift toward safer, non-replicating vaccines reflects a broader trend in vaccine development to balance efficacy with safety concerns. The legacy of smallpox eradication offers a blueprint for combating infectious diseases. By combining historical knowledge with modern scientific advancements, global health systems can remain vigilant against both natural outbreaks and potential bioterrorism threats. [39]

Conclusion

The eradication of smallpox stands as one of the greatest triumphs in global health history, demonstrating the power of coordinated vaccination efforts and surveillance systems. Despite its eradication, smallpox research remains relevant due to concerns about bioterrorism and the emergence of related orthopoxviruses, such as smallpox. [5] Advances in diagnostic tools, particularly PCR, have revolutionized the ability to detect and confirm variola virus infections, enhancing global preparedness. Vaccines have evolved from traditional live replicating forms like ACAM2000, which were effective but had safety concerns, to safer options such as JYNNEOS, which cater to vulnerable populations. [30] These developments not only reflect progress in virology but also the commitment to mitigating risks associated with re-emerging threats. Smallpox's legacy continues to inform strategies for controlling infectious diseases through mass vaccination and targeted interventions like ring vaccination. These lessons have been instrumental in addressing other outbreaks. [38] Moving forward, maintaining robust vaccine stockpiles, advancing antiviral research, and strengthening diagnostic infrastructure will be critical to safeguarding global health. The story of smallpox eradication is not just a historical achievement but a reminder of the potential for science and global cooperation to overcome even the most formidable challenges. [39]

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