



# Smallpox

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**Smallpox** was an infectious disease caused by either of two virus variants, *Variola major* and *Variola minor*.<sup>[1]</sup> The disease is also known by the Latin names *variola* or *variola vera*, derived from *varius* ("spotted") or *varus* ("pimple"). The disease was originally known in English as the "**pox**"<sup>[2]</sup> or "**red plague**";<sup>[3]</sup> the term "smallpox" was first used in Britain in the 15th century to distinguish variola from the "great pox" (syphilis).<sup>[4]</sup> The last naturally occurring case of smallpox (*Variola minor*) was diagnosed on 26 October 1977.<sup>[5]</sup>

Infection with smallpox is focused in small blood vessels of the skin and in the mouth and throat before disseminating. In the skin it results in a characteristic maculopapular rash and, later, raised fluid-filled blisters. *V. major* produced a more serious disease and had an overall mortality rate of 30–35 percent. *V. minor* caused a milder form of disease (also known as alastrim) which killed about 1 percent of those it infects.<sup>[6][7]</sup> Long-term complications of *V. major* infection included characteristic scars, commonly on the face, which occur in 65

**Smallpox**



A child infected with smallpox in Bangladesh, 1973. Patients with ordinary-type smallpox usually had bumps filled with a thick and opaque fluid, often with a depression or dimple in the center. This is a major distinguishing characteristic of the disease.

## Classification and external resources

<b>Specialty</b>	Infectious disease
<b>ICD-10</b>	B03 ( <a href="http://apps.who.int/classifications/icd10/browse/2016/en#/B03">http://apps.who.int/classifications/icd10/browse/2016/en#/B03</a> )
<b>ICD-9-CM</b>	050 ( <a href="http://www.icd9data.com/getICD9Code.aspx?icd9=050">http://www.icd9data.com/getICD9Code.aspx?icd9=050</a> )
<b>DiseasesDB</b>	12219 ( <a href="http://www.diseasesdatabase.com/ddb12219.htm">http://www.diseasesdatabase.com/ddb12219.htm</a> )
<b>MedlinePlus</b>	001356 ( <a href="https://medlineplus.gov/ency/article/001356.htm">https://medlineplus.gov/ency/article/001356.htm</a> )
<b>eMedicine</b>	emerg/885 ( <a href="http://www.emedicine.com/emerg/topic885.htm">http://www.emedicine.com/emerg/topic885.htm</a> )

–85 percent of survivors.<sup>[8]</sup> Blindness resulting from corneal ulceration and scarring, and limb deformities due to arthritis and osteomyelitis were less common complications, seen in about 2–5 percent of cases.

**Patient UK** Smallpox (<http://patient.info/doctor/Smallpox>)

**MeSH** *D012899* ([https://www.nlm.nih.gov/cgi/mesh/2016/MB\\_cgi?mode=&term=Smallpox&field=entry#TreeD012899](https://www.nlm.nih.gov/cgi/mesh/2016/MB_cgi?mode=&term=Smallpox&field=entry#TreeD012899))

Smallpox is believed to have emerged in human populations about 10,000 BC.<sup>[4]</sup> The earliest physical evidence of it is probably the pustular rash on the mummified body of Pharaoh Ramses V of Egypt.<sup>[9]</sup> The disease killed an estimated 400,000 Europeans annually during the closing years of the 18th century (including five reigning monarchs),<sup>[10]</sup> and was responsible for a third of all blindness.<sup>[6][11]</sup> Of all those infected, 20–60 percent—and over 80 percent of infected children—died from the disease.<sup>[12]</sup> Smallpox was responsible for an estimated 300–500 million deaths during the 20th century.<sup>[13][14][15]</sup> As recently as 1967, the World Health Organization (WHO) estimated that 15 million people contracted the disease and that two million died in that year.<sup>[5]</sup>

After vaccination campaigns throughout the 19th and 20th centuries, the WHO certified the global eradication of smallpox in 1979.<sup>[5]</sup> Smallpox is one of two infectious diseases to have been eradicated, the other being rinderpest, which was declared eradicated in 2011.<sup>[16][17][18]</sup>

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## Classification

There were two clinical forms of smallpox. *Variola major* was the severe and most common form, with a more extensive rash and higher fever. *Variola minor* was a less common presentation, and a much less severe disease, with historical death rates of 1 percent or less.<sup>[19]</sup> Subclinical (asymptomatic) infections with variola virus were noted but were not common.<sup>[20]</sup> In addition, a form called *variola sine eruptione* (smallpox without rash) was seen generally in vaccinated persons. This form was marked by a fever that occurred after the usual incubation period and could be confirmed only by antibody studies or, rarely, by virus isolation.<sup>[20]</sup>

## Signs and symptoms

The incubation period between contraction and the first obvious symptoms of the disease is around 12 days. Once inhaled, variola major virus invades the oropharyngeal (mouth and throat) or the respiratory mucosa, migrates to regional lymph nodes, and begins to multiply. In the initial growth phase the virus seems to move from cell to cell, but around the 12th day, lysis of many infected cells occurs and the virus is found in the bloodstream in large numbers (this is called *viremia*), and a second wave of multiplication occurs in the spleen, bone marrow, and lymph nodes. The initial or prodromal symptoms are similar to other viral diseases such as influenza and the common cold: fever of at least 38.3 °C (101 °F), muscle pain, malaise, headache and prostration. As the digestive tract is commonly involved, nausea and vomiting and backache often occur. The prodrome, or preeruptive stage, usually lasts 2–4 days. By days 12–15 the first visible lesions—small reddish spots called *enanthem*—appear on mucous membranes of the mouth, tongue, palate, and throat, and temperature falls to near normal. These lesions rapidly enlarge and rupture, releasing large amounts of virus into the saliva.<sup>[7]</sup>

Smallpox virus preferentially attacks skin cells, causing the characteristic pimples (called macules) associated with the disease. A rash develops on the skin 24 to 48 hours after lesions on the mucous membranes appear. Typically the macules first appear on the forehead, then rapidly spread to the whole face, proximal portions of extremities, the trunk, and lastly to



A child showing rash due to ordinary-type smallpox (*variola major*)

distal portions of extremities. The process takes no more than 24 to 36 hours, after which no new lesions appear.<sup>[7]</sup> At this point variola major infection can take several very different courses, resulting in four types of smallpox disease based on the Rao classification:<sup>[21]</sup> ordinary, modified, malignant (or flat), and hemorrhagic. Historically, smallpox has an overall fatality rate of about 30 percent; however, the malignant and hemorrhagic forms are usually fatal.<sup>[22]</sup>

## Ordinary

Ninety percent or more of smallpox cases among unvaccinated persons were of the ordinary type.<sup>[20]</sup> In this form of the disease, by the second day of the rash the macules became raised *papules*. By the third or fourth day the papules filled with an opalescent fluid to become *vesicles*. This fluid became opaque and turbid within 24–48 hours, giving them the appearance of pustules; however, the so-called pustules were filled with tissue debris, not pus.<sup>[7]</sup>

By the sixth or seventh day, all the skin lesions have become pustules. Between seven and ten days the pustules matured and reached their maximum size. The pustules were sharply raised, typically round, tense, and firm to the touch. The pustules were deeply embedded in the dermis, giving them the feel of a small bead in the skin. Fluid slowly leaked from the pustules, and by the end of the second week the pustules deflated, and started to dry up, forming crusts (or scabs). By day 16–20 scabs had formed over all the lesions, which have started to flake off, leaving depigmented scars.<sup>[23]</sup>

Ordinary smallpox generally produced a discrete rash, in which the pustules stood out on the skin separately. The distribution of the rash was densest on the face; denser on the extremities than on the trunk; and on the extremities, denser on the distal parts than on the proximal. The palms of the hands and soles of the feet were involved in the majority of cases. Sometimes, the blisters merged into sheets, forming a confluent rash, which began to detach the outer layers of skin from the underlying flesh. Patients with confluent smallpox often remained ill even after scabs have formed over all the lesions. In one case series, the case-fatality rate in confluent smallpox was 62 percent.<sup>[20]</sup>

## Modified

Referring to the character of the eruption and the rapidity of its development, modified smallpox occurred mostly in previously vaccinated people. In this form the prodromal illness still occurred but may be less severe than in the ordinary type. There is usually no fever during evolution of the rash. The skin lesions tended to be fewer and evolve more quickly, are more superficial, and may not show the uniform characteristic of more typical smallpox.<sup>[23]</sup> Modified smallpox was rarely, if ever, fatal. This form of variola major is more easily confused with chickenpox.<sup>[20]</sup>

## Malignant

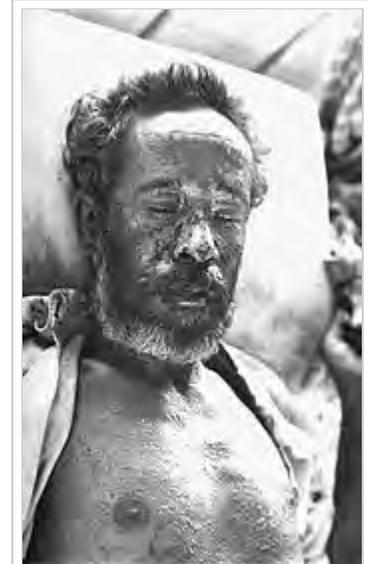
In malignant-type smallpox (also called flat smallpox) the lesions remained almost flush with the skin at the time when raised vesicles form in the ordinary type. It is unknown why some people developed this type. Historically, it accounted for 5–10 percent of cases, and the majority (72 percent) were children.<sup>[24]</sup> Malignant smallpox was accompanied by a severe prodromal phase that lasted 3–4 days, prolonged high

fever, and severe symptoms of toxemia. The rash on the tongue and palate was extensive. Skin lesions matured slowly and by the seventh or eighth day they were flat and appeared to be buried in the skin. Unlike ordinary-type smallpox, the vesicles contained little fluid, were soft and velvety to the touch, and may have contained hemorrhages. Malignant smallpox was nearly always fatal.<sup>[20]</sup>

## Hemorrhagic

Hemorrhagic smallpox is a severe form that is accompanied by extensive bleeding into the skin, mucous membranes, and gastrointestinal tract. This form develops in approximately 2 percent of infections and occurred mostly in adults.<sup>[20]</sup> In hemorrhagic smallpox the skin does not blister, but remains smooth. Instead, bleeding occurs under the skin, making it look charred and black,<sup>[20]</sup> hence this form of the disease is also known as black pox.<sup>[25]</sup>

In the early, or fulminating form, hemorrhaging appears on the second or third day as sub-conjunctival bleeding turns the whites of the eyes deep red. Hemorrhagic smallpox also produces a dusky erythema, petechiae, and hemorrhages in the spleen, kidney, serosa, muscle, and, rarely, the epicardium, liver, testes, ovaries and bladder. Death often occurs suddenly between the fifth and seventh days of illness, when only a few insignificant skin lesions are present. A later form of the disease occurs in patients who survive for 8–10 days. The hemorrhages appear in the early eruptive period, and the rash is flat and does not progress beyond the vesicular stage.<sup>[20]</sup> Patients in the early stage of disease show a decrease in coagulation factors (e.g. platelets, prothrombin, and globulin) and an increase in circulating antithrombin. Patients in the late stage have significant thrombocytopenia; however, deficiency of coagulation factors is less severe. Some in the late stage also show increased antithrombin.<sup>[7]</sup> This form of smallpox occurs in anywhere from 3 to 25 percent of fatal cases depending on the virulence of the smallpox strain.<sup>[22]</sup> Hemorrhagic smallpox is usually fatal.<sup>[20]</sup>



A man with severe hemorrhagic-type smallpox.

## Cause

Smallpox is caused by infection with variola virus, which belongs to the genus *Orthopoxvirus*, the family *Poxviridae* and subfamily *Chordopoxvirinae*.

## Evolution

The date of the appearance of smallpox is not settled. It most likely evolved from a rodent virus between 68,000 and 16,000 years ago.<sup>[26]</sup> The wide range of dates is due to the different records used to calibrate the molecular clock. One clade was the variola major strains (the more clinically severe form of

*Variola virus (Smallpox)*

smallpox) which spread from Asia between 400 and 1,600 years ago. A second clade included both *Alastrim minor* (a phenotypically mild smallpox) described from the American continents and isolates from West Africa which diverged from an ancestral strain between 1,400 and 6,300 years before present. This clade further diverged into two subclades at least 800 years ago.<sup>[27]</sup> A second estimate has placed the separation of variola from *Taterapox* at 3000–4000 years ago.<sup>[28]</sup> This is consistent with archaeological and historical evidence regarding the appearance of smallpox as a human disease which suggests a relatively recent origin. However, if the mutation rate is assumed to be similar to that of the herpesviruses, the divergence date between variola from *Taterapox* has been estimated to be 50,000 years ago.<sup>[28]</sup> While this is consistent with the other published estimates, it suggests that the archaeological and historical evidence is very incomplete. Better estimates of mutation rates in these viruses are needed.

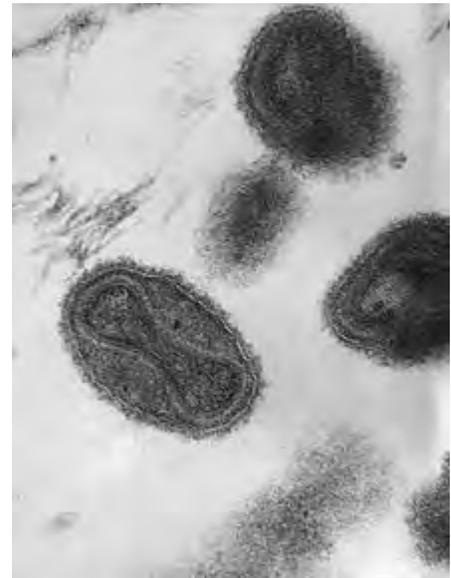
Examination of a strain that dates from ~1650 found that this strain was basal to the other presently sequenced strains.<sup>[29]</sup> The mutation rate of this virus is well modeled by a molecular clock. Diversification of strains only occurred in the 18th and 19th centuries.

## Virology

Variola is a large brick-shaped virus measuring approximately 302 to 350 nanometers by 244 to 270 nm,<sup>[30]</sup> with a single linear double stranded DNA genome 186 kilobase pairs (kbp) in size and containing a hairpin loop at each end.<sup>[31][32]</sup> The two classic varieties of smallpox are *variola major* and *variola minor*.

Four orthopoxviruses cause infection in humans: variola, vaccinia, cowpox, and monkeypox. Variola virus infects only humans in nature, although primates and other animals have been infected in a laboratory setting. Vaccinia, cowpox, and monkeypox viruses can infect both humans and other animals in nature.<sup>[20]</sup>

The life cycle of poxviruses is complicated by having multiple infectious forms, with differing mechanisms of cell entry. Poxviruses are unique among DNA viruses in that they replicate in the cytoplasm of the cell rather than in the nucleus. In order to replicate, poxviruses produce a variety of specialized proteins not produced by other DNA viruses, the most important of which is a viral-associated DNA-dependent RNA polymerase.



This transmission electron micrograph depicts a number of smallpox virions.

The "dumbbell-shaped" structure inside the virion is the viral core, which contains the viral DNA; Mag. = ~370,000x

### Virus classification

Group: Group I (dsDNA)  
 Order: *Unassigned*  
 Family: *Poxviridae*  
 Subfamily: *Chordopoxvirinae*  
 Genus: *Orthopoxvirus*

### Type species

*Vaccinia virus*

### Species

*Variola virus*

Both enveloped and unenveloped virions are infectious. The viral envelope is made of modified Golgi membranes containing viral-specific polypeptides, including hemagglutinin.<sup>[31]</sup> Infection with either variola major or variola minor confers immunity against the other.<sup>[7]</sup>

## Transmission

Transmission occurs through inhalation of airborne variola virus, usually droplets expressed from the oral, nasal, or pharyngeal mucosa of an infected person. It is transmitted from one person to another primarily through prolonged face-to-face contact with an infected person, usually within a distance of 6 feet (1.8 m), but can also be spread through direct contact with infected bodily fluids or contaminated objects (fomites) such as bedding or clothing. Rarely, smallpox has been spread by virus carried in the air in enclosed settings such as buildings, buses, and trains.<sup>[19]</sup> The virus can cross the placenta, but the incidence of congenital smallpox is relatively low.<sup>[7]</sup> Smallpox is not notably infectious in the prodromal period and viral shedding is usually delayed until the appearance of the rash, which is often accompanied by lesions in the mouth and pharynx. The virus can be transmitted throughout the course of the illness, but is most frequent during the first week of the rash, when most of the skin lesions are intact.<sup>[20]</sup> Infectivity wanes in 7 to 10 days when scabs form over the lesions, but the infected person is contagious until the last smallpox scab falls off.<sup>[33]</sup>

Smallpox is highly contagious, but generally spreads more slowly and less widely than some other viral diseases, perhaps because transmission requires close contact and occurs after the onset of the rash. The overall rate of infection is also affected by the short duration of the infectious stage. In temperate areas, the number of smallpox infections were highest during the winter and spring. In tropical areas, seasonal variation was less evident and the disease was present throughout the year.<sup>[20]</sup> Age distribution of smallpox infections depends on acquired immunity. Vaccination immunity declines over time and is probably lost within thirty years.<sup>[7]</sup> Smallpox is not known to be transmitted by insects or animals and there is no asymptomatic carrier state.<sup>[20]</sup>

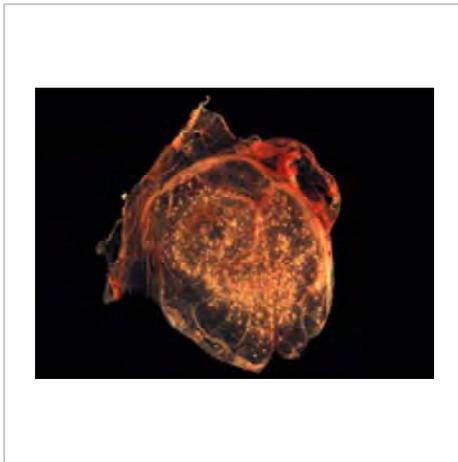
## Diagnosis

The clinical definition of smallpox is an illness with acute onset of fever equal to or greater than 38.3 °C (101 °F) followed by a rash characterized by firm, deep seated vesicles or pustules in the same stage of development without other apparent cause.<sup>[20]</sup> If a clinical case is observed, smallpox is confirmed using laboratory tests.

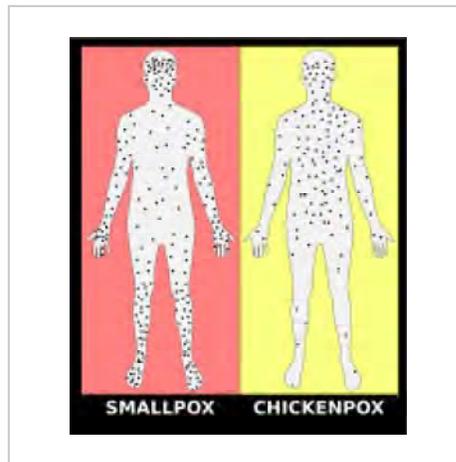
Microscopically, poxviruses produce characteristic cytoplasmic inclusions, the most important of which are known as Guarnieri bodies, and are the sites of viral replication. Guarnieri bodies are readily identified in skin biopsies stained with hematoxylin and eosin, and appear as pink blobs. They are found in virtually all poxvirus infections but the absence of Guarnieri bodies cannot be used to rule out smallpox.<sup>[34]</sup> The diagnosis of an orthopoxvirus infection can also be made rapidly by electron microscopic examination of pustular fluid or scabs. However, all orthopoxviruses exhibit identical brick-shaped virions by electron microscopy.<sup>[7]</sup> However, if particles with the characteristic morphology of herpesviruses are seen this will eliminate smallpox and other orthopoxvirus infections.

Definitive laboratory identification of variola virus involves growing the virus on chorioallantoic membrane (part of a chicken embryo) and examining the resulting pock lesions under defined temperature conditions.<sup>[35]</sup> Strains may be characterized by polymerase chain reaction (PCR) and restriction fragment length polymorphism (RFLP) analysis. Serologic tests and enzyme linked immunosorbent assays (ELISA), which measure variola virus-specific immunoglobulin and antigen have also been developed to assist in the diagnosis of infection.<sup>[36]</sup>

Chickenpox was commonly confused with smallpox in the immediate post-eradication era. Chickenpox and smallpox can be distinguished by several methods. Unlike smallpox, chickenpox does not usually affect the palms and soles. Additionally, chickenpox pustules are of varying size due to variations in the timing of pustule eruption: smallpox pustules are all very nearly the same size since the viral effect progresses more uniformly. A variety of laboratory methods are available for detecting chickenpox in evaluation of suspected smallpox cases.<sup>[20]</sup>



Smallpox virus lesions on the chorioallantoic membrane of a developing chick.



In contrast to the rash in smallpox, the rash in chickenpox occurs mostly on the torso, spreading less to the limbs.



An Italian female smallpox patient whose skin displayed the characteristics of late-stage confluent maculopapular scarring, 1965.

## Prevention

The earliest procedure used to prevent smallpox was inoculation (known as variolation after the introduction of smallpox vaccine to avoid possible confusion), which likely occurred in India, Africa, and China well before the practice arrived in Europe.<sup>[37]</sup> However, the idea that inoculation originated in India has been challenged, as few of the ancient Sanskrit medical texts described the process of inoculation.<sup>[38]</sup> Accounts of inoculation against smallpox in China can be found as early as the late 10th century, and the procedure was widely practiced by the 16th century, during the Ming dynasty.<sup>[39]</sup> If successful, inoculation produced lasting immunity to smallpox. However, because the person was

infected with variola virus, a severe infection could result, and the person could transmit smallpox to others. Variolation had a 0.5–2 percent mortality rate, considerably less than the 20–30 percent mortality rate of the disease.<sup>[20]</sup>

Lady Mary Wortley Montagu observed smallpox inoculation during her stay in the Ottoman Empire, writing detailed accounts of the practice in her letters, and enthusiastically promoted the procedure in England upon her return in 1718.<sup>[40]</sup> In 1721, Cotton Mather and colleagues provoked controversy in Boston by inoculating hundreds. In 1796, Edward Jenner, a doctor in Berkeley, Gloucestershire, rural England, discovered that immunity to smallpox could be produced by inoculating a person with material from a cowpox lesion. Cowpox is a poxvirus in the same family as variola. Jenner called the material used for inoculation vaccine, from the root word *vacca*, which is Latin for cow. The procedure was much safer than variolation, and did not involve a risk of smallpox transmission. Vaccination to prevent smallpox was soon practiced all over the world. During the 19th century, the cowpox virus used for smallpox vaccination was replaced by vaccinia virus. Vaccinia is in the same family as cowpox and variola, but is genetically distinct from both. The origin of vaccinia virus and how it came to be in the vaccine are not known.<sup>[20]</sup>



Components of a modern smallpox vaccination kit including the diluent, a vial of Dryvax vaccinia vaccine, and a bifurcated needle.



An 1802 cartoon of the early controversy surrounding Edward Jenner's vaccination theory, showing using his cowpox-derived smallpox vaccine causing cattle to emerge from patients.

The current formulation of smallpox vaccine is a live virus preparation of infectious vaccinia virus. The vaccine is given using a bifurcated (two-pronged) needle that is dipped into the vaccine solution. The needle is used to prick the skin (usually the upper arm) a number of times in a few seconds. If successful, a red and itchy bump develops at the vaccine site in three or four days. In the first week, the bump becomes a large blister (called a "Jennerian vesicle") which fills with pus, and begins to drain. During the second week, the blister begins to dry up and a scab forms. The scab falls off in the third week, leaving a small scar.<sup>[41]</sup>

The antibodies induced by vaccinia vaccine are cross-protective for other orthopoxviruses, such as monkeypox, cowpox, and variola (smallpox) viruses. Neutralizing antibodies are detectable 10 days after first-time vaccination, and seven days after revaccination. Historically, the vaccine has been effective in

preventing smallpox infection in 95 percent of those vaccinated.<sup>[42]</sup> Smallpox vaccination provides a high level of immunity for three to five years and decreasing immunity thereafter. If a person is vaccinated again later, immunity lasts even longer. Studies of smallpox cases in Europe in the 1950s and 1960s demonstrated that the fatality rate among persons vaccinated less than 10 years before exposure was 1.3 percent; it was 7 percent among those vaccinated 11 to 20 years prior, and 11 percent among those vaccinated 20 or more years prior to infection. By contrast, 52 percent of unvaccinated persons died.<sup>[43]</sup>

There are side effects and risks associated with the smallpox vaccine. In the past, about 1 out of 1,000 people vaccinated for the first time experienced serious, but non-life-threatening, reactions, including toxic or allergic reaction at the site of the vaccination (erythema multiforme), spread of the vaccinia virus to other parts of the body, and to other individuals. Potentially life-threatening reactions occurred in 14 to 500 people out of every 1 million people vaccinated for the first time. Based on past experience, it is estimated that 1 or 2 people in 1 million (0.000198 percent) who receive the vaccine may die as a result, most often the result of postvaccinial encephalitis or severe necrosis in the area of vaccination (called progressive vaccinia).

[42]



A demonstration by medical personnel on use of a bifurcated needle to deliver the smallpox vaccine, 2002.

Given these risks, as smallpox became effectively eradicated and the number of naturally occurring cases fell below the number of vaccine-induced illnesses and deaths, routine childhood vaccination was discontinued in the United States in 1972, and was abandoned in most European countries in the early 1970s.<sup>[5][44]</sup> Routine vaccination of health care workers was discontinued in the U.S. in 1976, and among military recruits in 1990 (although military personnel deploying to the Middle East and Korea still receive the vaccination<sup>[45]</sup>). By 1986, routine vaccination had ceased in all countries.<sup>[5]</sup> It is now primarily recommended for laboratory workers at risk for occupational exposure.<sup>[20]</sup>

## Treatment

Smallpox vaccination within three days of exposure will prevent or significantly lessen the severity of smallpox symptoms in the vast majority of people. Vaccination four to seven days after exposure can offer some protection from disease or may modify the severity of disease.<sup>[42]</sup> Other than vaccination, treatment of smallpox is primarily supportive, such as wound care and infection control, fluid therapy, and possible ventilator assistance. Flat and hemorrhagic types of smallpox are treated with the same therapies used to treat shock, such as fluid resuscitation. People with semi-confluent and confluent types of smallpox may have therapeutic issues similar to patients with extensive skin burns.<sup>[46]</sup>

No drug is currently approved for the treatment of smallpox. However, antiviral treatments have improved since the last large smallpox epidemics, and studies suggest that the antiviral drug cidofovir might be useful as a therapeutic agent. The drug must be administered intravenously, however, and may cause serious kidney toxicity.<sup>[47]</sup>

## Prognosis

The overall case-fatality rate for ordinary-type smallpox is about 30 percent, but varies by pock distribution: ordinary type-confluent is fatal about 50–75 percent of the time, ordinary-type semi-confluent about 25–50 percent of the time, in cases where the rash is discrete the case-fatality rate is less than 10 percent. The overall fatality rate for children younger than 1 year of age is 40–50 percent. Hemorrhagic and flat types have the highest fatality rates. The fatality rate for flat-type is 90 percent or

greater and nearly 100 percent is observed in cases of hemorrhagic smallpox. The case-fatality rate for variola minor is 1 percent or less.<sup>[23]</sup> There is no evidence of chronic or recurrent infection with variola virus.<sup>[23]</sup>

In fatal cases of ordinary smallpox, death usually occurs between the tenth and sixteenth days of the illness. The cause of death from smallpox is not clear, but the infection is now known to involve multiple organs. Circulating immune complexes, overwhelming viremia, or an uncontrolled immune response may be contributing factors.<sup>[20]</sup> In early hemorrhagic smallpox, death occurs suddenly about six days after the fever develops. Cause of death in hemorrhagic cases involved heart failure, sometimes accompanied by pulmonary edema. In late hemorrhagic cases, high and sustained viremia, severe platelet loss and poor immune response were often cited as causes of death.<sup>[24]</sup> In flat smallpox modes of death are similar to those in burns, with loss of fluid, protein and electrolytes beyond the capacity of the body to replace or acquire, and fulminating sepsis.<sup>[46]</sup>



A case of smallpox, 1886

## Complications

Complications of smallpox arise most commonly in the respiratory system and range from simple bronchitis to fatal pneumonia. Respiratory complications tend to develop on about the eighth day of the illness and can be either viral or bacterial in origin. Secondary bacterial infection of the skin is a relatively uncommon complication of smallpox. When this occurs, the fever usually remains elevated.<sup>[20]</sup>

Other complications include encephalitis (1 in 500 patients), which is more common in adults and may cause temporary disability; permanent pitted scars, most notably on the face; and complications involving the eyes (2 percent of all cases). Pustules can form on the eyelid, conjunctiva, and cornea, leading to complications such as conjunctivitis, keratitis, corneal ulcer, iritis, iridocyclitis, and optic atrophy. Blindness results in approximately 35 percent to 40 percent of eyes affected with keratitis and corneal ulcer. Hemorrhagic smallpox can cause subconjunctival and retinal hemorrhages. In 2 to 5 percent of young children with smallpox, virions reach the joints and bone, causing *osteomyelitis variolosa*. Lesions are symmetrical, most common in the elbows, tibia, and fibula, and characteristically cause separation of an epiphysis and marked periosteal reactions. Swollen joints limit movement, and arthritis may lead to limb deformities, ankylosis, malformed bones, flail joints, and stubby fingers.<sup>[7]</sup>

## History

### Disease emergence

The earliest credible clinical evidence of smallpox is found in the smallpox-like disease in medical writings from ancient India (as early as 1500 BC),<sup>[48][49]</sup> Egyptian mummy of Ramses V who died more than 3000 years ago (1145 BC)<sup>[9]</sup> and China (1122 BC).<sup>[50]</sup> It has been speculated that Egyptian traders brought smallpox to India during the 1st millennium BC, where it remained as an endemic human

disease for at least 2000 years. Smallpox was probably introduced into China during the 1st century AD from the southwest, and in the 6th century was carried from China to Japan.<sup>[24]</sup> In Japan, the epidemic of 735–737 is believed to have killed as much as one-third of the population.<sup>[10][51]</sup> At least seven religious deities have been specifically dedicated to smallpox, such as the god Sopona in the Yoruba religion. In India, the Hindu goddess of smallpox, Sitala Mata, was worshiped in temples throughout the country.<sup>[52]</sup>

One viewpoint is smallpox emerged 1588AD and the earlier reported cases were incorrectly identified as smallpox.<sup>[53][54]</sup>



Drawing accompanying text in Book XII of the 16th-century *Florentine Codex* (compiled 1540–1585), showing Nahuas of conquest-era central Mexico with smallpox.

The timing of the arrival of smallpox in Europe and southwestern Asia is less clear. Smallpox is not clearly described in either the Old or New Testaments of the Bible or in the literature of the Greeks or Romans. While some have identified the Plague of Athens—which was said to have originated in "Ethiopia" and Egypt—or the plague that lifted Carthage's 396 BC siege of Syracuse with smallpox,<sup>[2]</sup> many scholars agree it is very unlikely such a serious disease as *variola major* would have escaped being described by Hippocrates if it had existed in the Mediterranean region during his lifetime.<sup>[55]</sup> While the Antonine Plague that swept through the Roman Empire in AD 165–180 may have been caused by smallpox,<sup>[56]</sup> Saint Nicasius of Rheims became the patron saint of smallpox victims for having



Statue of Sopona, the Yoruba god thought to cause the disease.

supposedly survived a bout in 450,<sup>[2]</sup> and Saint Gregory of Tours recorded a similar outbreak in France and Italy in 580, the first use of the term *variola*;<sup>[2]</sup> other historians speculate that Arab armies first carried smallpox from Africa into Southwestern Europe during the 7th and 8th centuries.<sup>[24]</sup> In the 9th century the Persian physician, Rhazes, provided one of the most definitive descriptions of smallpox and was the first to differentiate smallpox from measles and chickenpox in his *Kitab fi al-jadari wa-al-hasbah* (*The Book of Smallpox and Measles*).<sup>[57]</sup> During the Middle Ages, smallpox made periodic incursions into Europe but did not become established there until the population increased and population movement became more active during the era of the Crusades. By the 16th century smallpox had become well established across most of Europe.<sup>[24]</sup> With its introduction into populated areas in India, China and Europe, smallpox affected mainly children, with periodic epidemics that killed as many as 30 percent of those infected. The settled existence of smallpox in Europe was of particular historical importance, since successive waves of exploration and colonization by Europeans tended to spread the disease to other parts of the world. By the 16th century it had become an important cause of morbidity and mortality throughout much of the world.<sup>[24]</sup>

There are no credible descriptions of smallpox-like disease in the Americas before the westward exploration by Europeans in the 15th century AD.<sup>[27]</sup> Smallpox was introduced into the Caribbean island of Hispaniola in 1509, and into the mainland in 1520, when Spanish settlers from Hispaniola arrived in Mexico bringing smallpox with them. Smallpox devastated the native Amerindian population and was an important factor in the conquest of the Aztecs and the Incas by the Spaniards.<sup>[24]</sup> Settlement of the east coast of North America in 1633 in Plymouth, Massachusetts was also accompanied by devastating outbreaks of smallpox among Native American populations,<sup>[58]</sup> and subsequently among the native-born colonists.<sup>[59]</sup> Case fatality rates during outbreaks in Native American populations were as high as 80–90%.<sup>[60]</sup> Smallpox was introduced into Australia in 1789 and again in 1829.<sup>[24]</sup> Although the disease was never endemic on the continent,<sup>[24]</sup> it was the principal cause of death in Aboriginal populations between 1780 and 1870.<sup>[61]</sup>



A smallpox sufferer in the United States, 1912

By the mid-18th century smallpox was a major endemic disease everywhere in the world except in Australia and in several small islands. In Europe smallpox was a leading cause of death in the 18th century, killing an estimated 400,000 Europeans each year.<sup>[62]</sup> Up to 10 percent of Swedish infants died of smallpox each year,<sup>[10]</sup> and the death rate of infants in Russia may have been even higher.<sup>[50]</sup> The widespread use of variolation in a few countries, notably Great Britain, its North American colonies, and China, somewhat reduced the impact of smallpox among the wealthy classes during the latter part of the 18th century, but a real reduction in its incidence did not occur until vaccination became a common practice toward the end of the 19th century. Improved vaccines and the practice of re-vaccination led to a substantial reduction in cases in Europe and North America, but smallpox remained almost unchecked everywhere else in the world. In the United States and South Africa a much milder form of smallpox, *variola minor*, was recognized just before the close of the 19th century. By the mid-20th century *variola minor* occurred along with *variola major*, in varying proportions, in many parts of Africa. Patients with *variola minor* experience only a mild systemic illness, are often ambulant throughout the course of the disease, and are therefore able to more easily spread disease. Infection with *v. minor* induces immunity against the more deadly *variola major* form. Thus as *v. minor* spread all over the USA, into Canada, the South American countries and Great Britain it became the dominant form of smallpox, further reducing mortality rates.<sup>[24]</sup>

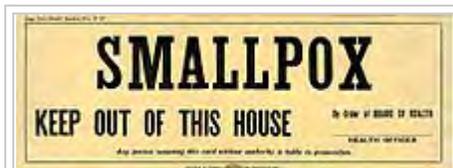
## Eradication

The English physician Edward Jenner demonstrated the effectiveness of cowpox to protect humans from smallpox in 1796, after which various attempts were made to eliminate smallpox on a regional scale. The introduction of the vaccine to the New World took place in Trinity, Newfoundland in 1800 by Dr. John Clinch, boyhood friend and medical colleague of Jenner.<sup>[63]</sup> As early as 1803, the Spanish Crown organized the Balmis expedition to transport the vaccine to the Spanish colonies in the Americas and the Philippines, and establish mass vaccination programs there.<sup>[64]</sup> The U.S. Congress passed the Vaccine Act of 1813 to ensure that safe smallpox vaccine would be available to the American public. By about

1817, a very solid state vaccination program existed in the Dutch East Indies.<sup>[65]</sup> In British India a program was launched to propagate smallpox vaccination, through Indian vaccinators, under the supervision of European officials.<sup>[66]</sup> Nevertheless, British vaccination efforts in India, and in Burma in particular, were hampered by stubborn indigenous preference for inoculation and distrust of vaccination, despite tough legislation, improvements in the local efficacy of the vaccine and vaccine preservative, and education efforts.<sup>[67]</sup> By 1832, the federal government of the United States established a smallpox vaccination program for Native Americans.<sup>[68]</sup> In 1842, the United Kingdom banned inoculation, later progressing to mandatory vaccination. The British government introduced compulsory smallpox vaccination by an Act of Parliament in 1853.<sup>[69]</sup> In the United States, from 1843 to 1855 first Massachusetts, and then other states required smallpox vaccination. Although some disliked these measures,<sup>[50]</sup> coordinated efforts against smallpox went on, and the disease continued to diminish in the wealthy countries. By 1897, smallpox had largely been eliminated from the United States.<sup>[70]</sup> In Northern Europe a number of countries had eliminated smallpox by 1900, and by 1914, the incidence in most industrialized countries had decreased to comparatively low levels. Vaccination continued in industrialized countries, until the mid to late 1970s as protection against reintroduction. Australia and New Zealand are two notable exceptions; neither experienced endemic smallpox and never vaccinated widely, relying instead on protection by distance and strict quarantines.<sup>[71]</sup>



Vaccination during the Smallpox Eradication and Measles Control Program in Niger, February 1969.



Smallpox quarantine order, California, c. 1910

The first hemisphere-wide effort to eradicate smallpox was made in 1950 by the Pan American Health Organization.<sup>[72]</sup> The campaign was successful in eliminating smallpox from all American countries except Argentina, Brazil, Colombia, and Ecuador.<sup>[71]</sup> In 1958 Professor Viktor Zhdanov, Deputy Minister of Health for the USSR, called on the World Health Assembly to undertake a global initiative to eradicate smallpox.<sup>[73]</sup> The

proposal (Resolution WHA11.54) was accepted in 1959.<sup>[73]</sup> At this point, 2 million people were dying from smallpox every year. Overall, however, the progress towards eradication was disappointing, especially in Africa and in the Indian subcontinent. In 1966 an international team, the Smallpox Eradication Unit, was formed under the leadership of an American, Donald Henderson.<sup>[74]</sup> In 1967, the World Health Organization intensified the global smallpox eradication by contributing \$2.4 million annually to the effort, and adopted the new disease surveillance method promoted by Czech epidemiologist Karel Raška.<sup>[75][76]</sup>

In the early 1950s an estimated 50 million cases of smallpox occurred in the world each year.<sup>[5]</sup> To eradicate smallpox, each outbreak had to be stopped from spreading, by isolation of cases and vaccination of everyone who lived close by. This process is known as "ring vaccination". The key to this strategy was the monitoring of cases in a community (known as surveillance) and containment. The initial problem the WHO team faced was inadequate reporting of smallpox cases, as many cases did not

come to the attention of the authorities. The fact that humans are the only reservoir for smallpox infection, and that carriers did not exist, played a significant role in the eradication of smallpox. The WHO established a network of consultants who assisted countries in setting up surveillance and containment activities. Early on, donations of vaccine were provided primarily by the Soviet Union and the United States, but by 1973, more than 80 percent of all vaccine was produced in developing countries.<sup>[71]</sup>

The last major European outbreak of smallpox was in 1972 in Yugoslavia, after a pilgrim from Kosovo returned from the Middle East, where he had contracted the virus. The epidemic infected 175 people, causing 35 deaths. Authorities declared martial law, enforced quarantine, and undertook widespread re-vaccination of the population, enlisting the help of the WHO. In two months, the outbreak was over.<sup>[77]</sup> Prior to this, there had been a smallpox outbreak in May–July 1963 in Stockholm, Sweden, brought from the Far East by a Swedish sailor; this had been dealt with by quarantine measures and vaccination of the local population.<sup>[78]</sup>



Two-year-old Rahima Banu of Bangladesh (pictured) was the last person infected with naturally occurring *Variola major*, in 1975

By the end of 1975, smallpox persisted only in the Horn of Africa. Conditions were very difficult in Ethiopia and Somalia, where there were few roads. Civil war, famine, and refugees made the task even more difficult. An intensive surveillance and containment and vaccination program was undertaken in these countries in early and mid-1977, under the direction of Australian microbiologist Frank Fenner. As the campaign neared its goal, Fenner and his team played an important role in verifying eradication.<sup>[79]</sup> The last naturally occurring case of indigenous smallpox (*Variola minor*) was diagnosed in Ali Maow Maalin, a hospital cook in Merca, Somalia, on 26 October 1977.<sup>[20]</sup> The last naturally occurring case of the more deadly *Variola major* had been detected in October 1975 in a two-year-old Bangladeshi girl, Rahima Banu.<sup>[25]</sup>

The global eradication of smallpox was certified, based on intense verification activities in countries, by a commission of eminent scientists on 9 December 1979 and subsequently endorsed by the World Health Assembly on 8 May 1980.<sup>[5][80]</sup> The first two sentences of the resolution read:

Having considered the development and results of the global program on smallpox eradication initiated by WHO in 1958 and intensified since 1967 ... Declares solemnly that the world and its peoples have won freedom from smallpox, which was a most devastating disease sweeping in epidemic form through many countries since earliest time, leaving death, blindness and disfigurement in its wake and which only a decade ago was rampant in Africa, Asia and South America.

— World Health Organization, Resolution WHA33.3<sup>[81]</sup>

## Post-eradication

The last cases of smallpox in the world occurred in an outbreak of two cases (one of which was fatal) in Birmingham, UK in 1978. A medical photographer, Janet Parker, contracted the disease at the University of Birmingham Medical School and died on September 11, 1978,<sup>[81]</sup> after which Professor Henry Bedson, the scientist responsible for smallpox research at the university, committed suicide.<sup>[4][82]</sup> All known stocks of smallpox were subsequently destroyed or transferred to two WHO-designated reference laboratories with BSL-4 facilities—the United States' Centers for Disease Control and Prevention and Russia's State Research Center of Virology and Biotechnology VECTOR.<sup>[83]</sup>

WHO first recommended destruction of the virus in 1986 and later set the date of destruction to be 30 December 1993. This was postponed to 30 June 1999.<sup>[84]</sup> Due to resistance from the U.S. and Russia, in 2002 the World Health Assembly agreed to permit the temporary retention of the virus stocks for specific research purposes.<sup>[85]</sup> Destroying existing stocks would reduce the risk involved with ongoing smallpox research; the stocks are not needed to respond to a smallpox outbreak.<sup>[86]</sup> Some scientists have argued that the stocks may be useful in developing new vaccines, antiviral drugs, and diagnostic tests;<sup>[87]</sup> however, a 2010 review by a team of public health experts appointed by WHO concluded that no essential public health purpose is served by the U.S. and Russia continuing to retain virus stocks.<sup>[88]</sup> The latter view is frequently supported in the scientific community, particularly among veterans of the WHO Smallpox Eradication Program.<sup>[89]</sup>

In March 2004 smallpox scabs were found inside an envelope in a book on Civil War medicine in Santa Fe, New Mexico.<sup>[90]</sup> The envelope was labeled as containing scabs from a vaccination and gave scientists at the Centers for Disease Control and Prevention an opportunity to study the history of smallpox vaccination in the U.S.

In July 2014 several vials of smallpox were discovered in an FDA laboratory at the National Institutes of Health location in Bethesda, Maryland.<sup>[91]</sup>

## Society and culture

### Biological warfare

The British used smallpox as a biological warfare agent at the Siege of Fort Pitt during the French and Indian Wars (1754–1763) against France and its Native American allies.<sup>[92][93]</sup> The actual use of smallpox had official sanction. British officers, including the top British commanding generals, ordered, sanctioned, paid for and conducted the use of smallpox against the Native Americans. As described by



Three former directors of the Global Smallpox Eradication Program read the news that smallpox had been globally eradicated, 1980

historians, "there is no doubt that British military authorities approved of attempts to spread smallpox among the enemy", and "it was deliberate British policy to infect the indians with smallpox".<sup>[94]</sup> On June 24, 1763, William Trent, a local trader and commander of the Fort Pitt militia, wrote, "Out of our regard for them, we gave them two Blankets and an Handkerchief out of the Small Pox Hospital. I hope it will have the desired effect."<sup>[95][96]</sup> The effectiveness of this effort to broadcast the disease is unknown. There are also accounts that smallpox was used as a weapon during the American Revolutionary War (1775–1783).<sup>[97][98]</sup>

According to a theory put forward in *Journal of Australian Studies* (JAS) by an independent researcher, in 1789, British marines used smallpox against indigenous tribes in New South Wales.<sup>[99]</sup> This occasion was also discussed earlier in *Bulletin of the History of Medicine*<sup>[100]</sup> and by David Day in his book *Claiming a Continent: A New History of Australia*.<sup>[101]</sup> Prior to the JAS article this theory was disputed by some academics.<sup>[102]</sup> Jack Carmody claimed the cause of the outbreak in question was more likely due to chickenpox, which at the time was sometimes identified as a mild form of smallpox. While it was noted that, in the 8-month voyage of the First Fleet and the following 14 months there were no reports of smallpox amongst the colonists and that as smallpox has an incubation period of 10–12 days it is unlikely it was present in the first fleet, it is now known that the likely source was bottles of smallpox virus possessed by First Fleet surgeons and there actually was a report of smallpox amongst the colonists - a seaman, Jefferies. More information is at: First Fleet Smallpox.

During World War II, scientists from the United Kingdom, United States and Japan (Unit 731 of the imperial Japanese army) were involved in research into producing a biological weapon from smallpox.<sup>[103]</sup> Plans of large scale production were never carried through as they considered that the weapon would not be very effective due to the wide-scale availability of a vaccine.<sup>[97]</sup>

In 1947 the Soviet Union established a smallpox weapons factory in the city of Zagorsk, 75 km to the northeast of Moscow.<sup>[104]</sup> An outbreak of weaponized smallpox occurred during testing at a facility on an island in the Aral Sea in 1971. General Prof. Peter Burgasov, former Chief Sanitary Physician of the Soviet Army and a senior researcher within the Soviet program of biological weapons, described the incident:

On Vozrozhdeniya Island in the Aral Sea, the strongest recipes of smallpox were tested. Suddenly I was informed that there were mysterious cases of mortalities in Aralsk. A research ship of the Aral fleet came to within 15 km of the island (it was forbidden to come any closer than 40 km). The lab technician of this ship took samples of plankton twice a day from the top deck. The smallpox formulation—400 gr. of which was exploded on the island—"got her" and she became infected. After returning home to Aralsk, she infected several people including children. All of them died. I suspected the reason for this and called the Chief of General Staff of Ministry of Defense and requested to forbid the stop of the Alma-Ata—Moscow train in Aralsk. As a result, the epidemic around the country was prevented. I called Andropov, who at that time was Chief of KGB, and informed him of the exclusive recipe of smallpox obtained on Vozrazhdenie Island.<sup>[105][106]</sup>

Others contend that the first patient may have contracted the disease while visiting Uyaly or Komsomolsk-on-Ustyurt, two cities where the boat docked.<sup>[107][108]</sup>

Responding to international pressures, in 1991 the Soviet government allowed a joint U.S.-British inspection team to tour four of its main weapons facilities at Biopreparat. The inspectors were met with evasion and denials from the Soviet scientists, and were eventually ordered out of the facility.<sup>[109]</sup> In 1992 Soviet defector Ken Alibek alleged that the Soviet bioweapons program at Zagorsk had produced a large stockpile—as much as twenty tons—of weaponized smallpox (possibly engineered to resist vaccines, Alibek further alleged), along with refrigerated warheads to deliver it. Alibek's stories about the former Soviet program's smallpox activities have never been independently verified.

In 1997, the Russian government announced that all of its remaining smallpox samples would be moved to the Vector Institute in Koltsovo.<sup>[109]</sup> With the breakup of the Soviet Union and unemployment of many of the weapons program's scientists, U.S. government officials have expressed concern that smallpox and the expertise to weaponize it may have become available to other governments or terrorist groups who might wish to use virus as means of biological warfare.<sup>[110]</sup> Specific allegations made against Iraq in this respect, however, proved to be mistaken.<sup>[111]</sup>

Concern has been expressed by some that artificial gene synthesis could be used to recreate the virus from existing digital genomes, for use in biological warfare.<sup>[112]</sup> Insertion of the synthesized smallpox DNA into existing related pox viruses could theoretically be used to recreate the virus.<sup>[112]</sup> The first step to mitigating this risk, it has been suggested, should be to destroy the remaining virus stocks so as to enable unequivocal criminalization of any possession of the virus.<sup>[113]</sup>

## Notable cases

Famous historical figures who contracted smallpox include Lakota Chief Sitting Bull, Ramses V of Egypt,<sup>[114]</sup> the Kangxi Emperor (survived), Shunzhi Emperor and Tongzhi Emperor (refer to the official history) of China, Date Masamune of Japan (who lost an eye to the disease). Cuitláhuac, the 10th tlatoani (ruler) of the Aztec city of Tenochtitlan, died of smallpox in 1520, shortly after its introduction to the Americas, and the Incan emperor Huayna Capac died of it in 1527. More recent public figures include Guru Har Krishan, 8th Guru of the Sikhs, in 1664, Peter II of Russia in 1730 (died),<sup>[115]</sup> George Washington (survived), king Louis XV in 1774 (died) and Maximilian III Joseph, Elector of Bavaria in 1777.

Prominent families throughout the world often had several people infected by and/or perish from the disease. For example, several relatives of Henry VIII survived the disease but were scarred by it. These include his sister Margaret, Queen of Scotland, his fourth wife, Anne of Cleves, and his two daughters: Mary I of England in 1527 and Elizabeth I of England in 1562 (as an adult she would often try to disguise the pockmarks with heavy makeup). His great-niece, Mary, Queen of Scots, contracted the disease as a child but had no visible scarring.

In Europe, deaths from smallpox often changed dynastic succession. The only surviving son of Henry VIII, Edward VI, died from complications shortly after apparently recovering from the disease, thereby nullifying Henry's efforts to ensure a male successor to the throne (his two immediate successors were



## Tradition and religion

In the face of the devastation of smallpox, various smallpox gods and goddesses have been worshipped throughout parts of the Old World, for example in China and in India. In China, the smallpox goddess was referred to as T'ou-Shen Niang-Niang.<sup>[121]</sup> Chinese believers actively worked to appease the goddess and pray for her mercy, by such measures as referring to smallpox pustules as "beautiful flowers" as a euphemism intended to avert offending the goddess, for example.<sup>[122]</sup> In a related New Year's Eve custom it was prescribed that the children of the house wear ugly masks while sleeping, so as to conceal any beauty and thereby avoid attracting the goddess, who would be passing through sometime that night.<sup>[122]</sup> If a case of smallpox did occur, shrines would be set up in the homes of the victims, to be worshipped and offered to as the disease ran its course. If the victim recovered, the shrines were removed and carried away in a special paper chair or boat for burning. If the patient did not recover, the shrine was destroyed and cursed, so as to expel the goddess from the house.<sup>[121]</sup>



The Hindu goddess Shitala was worshipped to prevent or cure smallpox.

India's first records of smallpox can be found in a medical book that dates back to A.D. 400. This book describes a disease that sounds exceptionally like smallpox.<sup>[122]</sup> India, like China, created a goddess in response to its exposure to smallpox. The Hindu goddess Shitala was both worshipped and feared during her reign. It was believed that this goddess was both evil and kind and had the ability to inflict victims when angered, as well as calm the fevers of the already afflicted.<sup>[123]</sup> Portraits of the goddess show her holding a broom in her right hand to continue to move the disease and a pot of cool water in the other hand in an attempt to soothe victims.<sup>[122]</sup> Shrines were created where many India natives, both healthy and not, went to worship and attempt to protect themselves from this disease. Some Indian women, in an attempt to ward off Shitala, placed plates of cooling foods and pots of water on the roofs of their homes.<sup>[124]</sup>

In cultures that did not recognize a smallpox deity, there was often nonetheless a belief in smallpox demons, who were accordingly blamed for the disease. Such beliefs were prominent in Japan, Europe, Africa, and other parts of the world. Nearly all cultures who believed in the demon also believed that it was afraid of the color red. This led to the invention of so-called red treatment, where victims and their rooms would be decorated in red. The practice spread to Europe in the 12th century and was practiced by (among others) Charles V of France and Elizabeth I of England.<sup>[2]</sup> Afforded scientific credibility through the studies by Finsen showing that red light reduced scarring,<sup>[2]</sup> this belief persisted even until the 1930s.

## See also

- 1837 Great Plains smallpox epidemic

- Aral smallpox incident
- Biological warfare
- CCR5-Δ32
- Columbian Exchange
- First Nations
- Herd immunity
- List of cutaneous conditions
- List of epidemics
- Mathematics of mass vaccination
- Pandemic
- Population history of indigenous peoples of the Americas
- *Smallpox 2002*—film
- Smallpox demon
- *What the Ancients Did for Us*—a BBC documentary highlighting ancient inoculation procedures in India

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## External links

- Image of Amhearst letter to Colonel Henry Bouquet – give smallpox to Indians. ([http://cherokeeregistry.com/index.php?option=com\\_content&view=article&id=407&Itemid=617](http://cherokeeregistry.com/index.php?option=com_content&view=article&id=407&Itemid=617))
- Smallpox Biosafety: A Website About Destruction of Smallpox Virus Stocks (<http://www.smallpoxbiosafety.org>)
- Detailed CIDRAP Smallpox overview (<http://www.cidrap.umn.edu/cidrap/content/bt/smallpox/biofacts/index.html>)
- Agent Fact Sheet: Smallpox ([http://www.upmc-biosecurity.org/website/focus/agents\\_diseases/fact\\_sheets/smallpox.html](http://www.upmc-biosecurity.org/website/focus/agents_diseases/fact_sheets/smallpox.html)), Center for Biosecurity
- Smallpox Images and Diagnosis Synopsis (<http://www.logicalimages.com/resourcesBTAgentsSmallpox.htm>)
- Variola Virus Genomes ([http://www.poxvirus.org/query.asp?web\\_taxonomy=variola%20virus](http://www.poxvirus.org/query.asp?web_taxonomy=variola%20virus)) database search results from the Poxvirus Bioinformatics Resource Center
- Virus Pathogen Database and Analysis Resource (ViPR): Poxviridae (<http://www.viprbrc.org/brc/home.do?decorator=pox>)

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