[Template:Redirect](/wiki/Template:Redirect" \o "Template:Redirect) [Template:Pp-move-indef](/wiki/Template:Pp-move-indef) [Template:Pp-semi-indef](/wiki/Template:Pp-semi-indef) [Template:Infobox medical condition](/wiki/Template:Infobox_medical_condition)

**Smallpox** was an [infectious disease](/wiki/Infectious_disease) caused by either of two [virus](/wiki/Virus_(biology)) variants, *Variola major* and *Variola minor*.<ref name=Sherris>[Template:Cite book](/wiki/Template:Cite_book)</ref> The disease is also known by the [Latin](/wiki/Latin) names ***Variola*** or *Variola vera*, derived from *varius* ("spotted") or *varus* ("pimple"). The disease was originally known in English as the "**pox**"<ref name=SmaPoHist/> or "**red plague**";[[1]](#cite_note-1) the term "smallpox" was first used in Britain in the 15th century to distinguish variola from the "great pox" ([syphilis](/wiki/Syphilis)).<ref name=Barquet>[Template:Cite journal](/wiki/Template:Cite_journal)</ref> The last naturally occurring case of smallpox (*Variola minor*) was diagnosed on 26 October 1977.<ref name=WHO\_Factsheet>[Template:Cite web](/wiki/Template:Cite_web)</ref>

Infection with smallpox is focused in small [blood vessels](/wiki/Blood_vessel) of the skin and in the mouth and throat before disseminating. In the skin it results in a characteristic [maculopapular rash](/wiki/Maculopapular_rash) and, later, raised fluid-filled [blisters](/wiki/Blister). *V. major* produced a more serious disease and had an overall [mortality rate](/wiki/Mortality_rate) of 30–35 percent. *V. minor* caused a milder form of disease (also known as [**alastrim**](/wiki/Alastrim), **cottonpox**, **milkpox**, **whitepox**, and **Cuban itch**) which killed about 1 percent of its victims.<ref name=Behbehani\_1983>[Template:Cite journal](/wiki/Template:Cite_journal)</ref><ref name=AFIP/> Long-term complications of *V. major* infection included characteristic scars, commonly on the face, which occur in 65–85 percent of survivors.[[2]](#cite_note-2) [Blindness](/wiki/Blindness) resulting from [corneal ulceration](/wiki/Corneal_ulcer) and scarring, and limb deformities due to arthritis and [osteomyelitis](/wiki/Osteomyelitis) were less common complications, seen in about 2–5 percent of cases.

Smallpox is believed to have emerged in [human populations](/wiki/Human_population) about 10,000 BC.<ref name=Barquet/> The earliest physical evidence of it is probably the pustular rash on the mummified body of Pharaoh [Ramses V](/wiki/Ramses_V) of Egypt.<ref name=Ramses>[Template:Cite web](/wiki/Template:Cite_web)</ref> The disease killed an estimated 400,000 Europeans annually during the closing years of the 18th century (including five reigning [monarchs](/wiki/Monarch)),<ref name=Hays>J. N. Hays (2005). "[*Epidemics and pandemics: their impacts on human history*](https://books.google.com/books?id=GyE8Qt-kS1kC&pg=PA151&dq=&lr=&hl=en&cd=23#v=onepage&q=false)". ABC-CLIO. p.151. ISBN 1-85109-658-2</ref> and was responsible for a third of all blindness.<ref name=Behbehani\_1983/>[[3]](#cite_note-3) Of all those infected, 20–60 percent—and over 80 percent of infected children—died from the disease.[[4]](#cite_note-4) Smallpox was responsible for an estimated 300–500 million deaths during the 20th century.[[5]](#cite_note-5)[[6]](#cite_note-6)[[7]](#cite_note-7) As recently as 1967, the [World Health Organization](/wiki/World_Health_Organization) (WHO) estimated that 15 million people contracted the disease and that two million died in that year.<ref name=WHO\_Factsheet/>

After [vaccination](/wiki/Vaccination) campaigns throughout the 19th and 20th centuries, the WHO certified the [global eradication](/wiki/Eradication_of_infectious_diseases) of smallpox in 1979.[[8]](#cite_note-8) Smallpox is one of two [infectious diseases](/wiki/Infectious_disease) to have been eradicated, the other being [rinderpest](/wiki/Rinderpest), which was declared eradicated in 2011.[[9]](#cite_note-9)[[10]](#cite_note-10)[[11]](#cite_note-11)

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## Classification[[edit](/index.php?title=(none)&action=edit&section=1)]

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](/wiki/Alastrim) was a less common presentation, and a much less severe disease, with historical death rates of 1 percent or less.<ref name=FactSheet>[Template:Cite web](/wiki/Template:Cite_web)</ref> Subclinical ([asymptomatic](/wiki/Asymptomatic)) infections with variola virus were noted but were not common.<ref name= PinkBook/> 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.<ref name= PinkBook/>

## Signs and symptoms[[edit](/index.php?title=(none)&action=edit&section=2)]

[thumb|A child showing rash due to ordinary-type smallpox (variola major)](/wiki/File:Smallpox_child.jpg) The [incubation period](/wiki/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](/wiki/Respiratory) mucosa, migrates to regional [lymph nodes](/wiki/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](/wiki/Lysis) of many infected cells occurs and the virus is found in the [bloodstream](/wiki/Blood) in large numbers (this is called [*viremia*](/wiki/Viremia)), and a second wave of multiplication occurs in the spleen, [bone marrow](/wiki/Bone_marrow), and lymph nodes. The initial or prodromal symptoms are similar to other viral diseases such as [influenza](/wiki/Influenza) and the [common cold](/wiki/Common_cold): [fever](/wiki/Fever) of at least [Template:Convert](/wiki/Template:Convert), [muscle pain](/wiki/Myalgia), malaise, headache and [prostration](/wiki/Prostration). As the [digestive tract](/wiki/Gastrointestinal_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*](/wiki/Enanthem)—appear on mucous membranes of the mouth, tongue, [palate](/wiki/Palate), and throat, and temperature falls to near normal. These lesions rapidly enlarge and rupture, releasing large amounts of virus into the [saliva](/wiki/Saliva).<ref name= AFIP/>

Smallpox virus preferentially attacks skin cells, causing the characteristic pimples (called [macules](/wiki/Macule)) 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 distal portions of extremities. The process takes no more than 24 to 36 hours, after which no new lesions appear.<ref name= AFIP/> At this point variola major infection can take several very different courses, resulting in four types of smallpox disease based on the Rao classification:[[12]](#cite_note-12) ordinary, modified, malignant (or flat), and hemorrhagic. Historically, smallpox has an overall [fatality rate](/wiki/Fatality_rate) of about 30 percent; however, the malignant and hemorrhagic forms are usually fatal.<ref name=eMedicine\_Smallpox>[Template:Cite web](/wiki/Template:Cite_web)</ref>

### Ordinary[[edit](/index.php?title=(none)&action=edit&section=3)]

Ninety percent or more of smallpox cases among unvaccinated persons were of the ordinary type.<ref name= PinkBook/> In this form of the disease, by the second day of the rash the macules became raised [*papules*](/wiki/Papule). By the third or fourth day the papules filled with an opalescent fluid to become [*vesicles*](/wiki/Vesicle_(dermatology)). This fluid became [opaque](/wiki/Opacity_(optics)) and [turbid](/wiki/Turbid) within 24–48 hours, giving them the appearance of [pustules](/wiki/Pustule); however, the so-called pustules were filled with tissue debris, not pus.<ref name= AFIP/>

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](/wiki/Depigmentation) scars.<ref name=training1>[Template:Cite web](/wiki/Template:Cite_web)</ref>

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.<ref name= PinkBook/>

### Modified[[edit](/index.php?title=(none)&action=edit&section=4)]

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.<ref name=training1/> Modified smallpox was rarely, if ever, fatal. This form of variola major is more easily confused with [chickenpox](/wiki/Chickenpox).<ref name= PinkBook/>

### Malignant[[edit](/index.php?title=(none)&action=edit&section=5)]

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.<ref name= Fenner1>[Template:Cite book](/wiki/Template:Cite_book)</ref> Malignant smallpox was accompanied by a severe [prodromal](/wiki/Prodromal) phase that lasted 3–4 days, prolonged high fever, and severe symptoms of [toxemia](/wiki/Bacteremia). 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.<ref name= PinkBook/>

### Hemorrhagic[[edit](/index.php?title=(none)&action=edit&section=6)]

[thumb|upright|A man with severe hemorrhagic-type smallpox.](/wiki/File:Hemorrhagic_smallpox.jpg) [Hemorrhagic](/wiki/Hemorrhagic) smallpox is a severe form that is accompanied by extensive [bleeding into](/wiki/Internal_bleeding) the skin, mucous membranes, and gastrointestinal tract. This form develops in approximately 2 percent of infections and occurred mostly in adults.<ref name= PinkBook/> In hemorrhagic smallpox the skin does not blister, but remains smooth. Instead, bleeding occurs under the skin, making it look charred and black,<ref name= PinkBook/> hence this form of the disease is also known as [black pox](/wiki/Black_pox).<ref name=PrestonNY/>

In the early, or fulminating form, hemorrhaging appears on the second or third day as sub-[conjunctival](/wiki/Conjunctival) bleeding turns the whites of the eyes deep red. Hemorrhagic smallpox also produces a dusky [erythema](/wiki/Erythema), [petechiae](/wiki/Petechiae), and hemorrhages in the spleen, kidney, [serosa](/wiki/Serosa), muscle, and, rarely, the [epicardium](/wiki/Epicardium), [liver](/wiki/Liver), [testes](/wiki/Testes), [ovaries](/wiki/Ovaries) and [bladder](/wiki/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.<ref name= PinkBook/> Patients in the early stage of disease show a decrease in [coagulation factors](/wiki/Coagulation_factor) (e.g. [platelets](/wiki/Platelet), [prothrombin](/wiki/Prothrombin), and [globulin](/wiki/Globulin)) and an increase in circulating [antithrombin](/wiki/Antithrombin). Patients in the late stage have significant [thrombocytopenia](/wiki/Thrombocytopenia); however, deficiency of coagulation factors is less severe. Some in the late stage also show increased antithrombin.<ref name= AFIP/> This form of smallpox occurs in anywhere from 3 to 25 percent of fatal cases depending on the virulence of the smallpox strain.<ref name=eMedicine\_Smallpox/> Hemorrhagic smallpox is usually fatal.<ref name= PinkBook/>

## Cause[[edit](/index.php?title=(none)&action=edit&section=7)]

### Pathogens[[edit](/index.php?title=(none)&action=edit&section=8)]

[Template:Taxobox](/wiki/Template:Taxobox) Smallpox is caused by infection with variola virus, which belongs to the genus [Orthopoxvirus](/wiki/Orthopoxvirus), the family [Poxviridae](/wiki/Poxviridae) and subfamily chordopoxvirinae.

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.<ref name=Esposito2006>[Template:Cite journal](/wiki/Template:Cite_journal)</ref> The wide range of dates is due to the different records used to calibrate the molecular clock. One [clade](/wiki/Clade) was the variola major strains (the more clinically severe form of 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.<ref name=Li2007>[Template:Cite journal](/wiki/Template:Cite_journal)</ref> A second estimate has placed the separation of variola from [Taterapox](/wiki/Taterapox) at 3000–4000 years ago.<ref name=Hughes2010>[Template:Cite journal](/wiki/Template:Cite_journal)</ref> 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](/wiki/Herpesvirus), the divergence date between variola from Taterapox has been estimated to be 50,000 years ago.[[13]](#cite_note-13) 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.

Variola is a large brick-shaped virus measuring approximately 302 to 350 [nanometers](/wiki/Nanometer) by 244 to 270 nm,[[14]](#cite_note-14) with a single linear [double stranded DNA](/wiki/DsDNA) [genome](/wiki/Genome) 186 [kilobase pairs](/wiki/Kilobase_pair) (kbp) in size and containing a [hairpin loop](/wiki/Hairpin_loop) at each end.<ref name=Moss>[Template:Cite book](/wiki/Template:Cite_book)</ref><ref name=Damon>[Template:Cite book](/wiki/Template:Cite_book)</ref> The two classic varieties of smallpox are variola major and variola minor.

Four orthopoxviruses cause infection in humans: variola, [vaccinia](/wiki/Vaccinia), [cowpox](/wiki/Cowpox), and [monkeypox](/wiki/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.<ref name = PinkBook>[Template:Cite book](/wiki/Template:Cite_book)</ref>

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](/wiki/Cytoplasm) of the cell rather than in the [nucleus](/wiki/Cell_nucleus). In order to replicate, poxviruses produce a variety of specialized proteins not produced by other [DNA viruses](/wiki/DNA_viruses), the most important of which is a viral-associated [DNA-dependent RNA polymerase](/wiki/DNA-dependent_RNA_polymerase).

Both [enveloped](/wiki/Viral_envelope) and unenveloped virions are infectious. The viral envelope is made of modified [Golgi](/wiki/Golgi_apparatus) membranes containing viral-specific polypeptides, including [hemagglutinin](/wiki/Hemagglutinin).<ref name=Moss/> Infection with either variola major or variola minor confers immunity against the other.<ref name=AFIP>[Template:Cite web](/wiki/Template:Cite_web)</ref>

### Transmission[[edit](/index.php?title=(none)&action=edit&section=9)]

Transmission occurs through inhalation of [airborne](/wiki/Airborne_disease) variola virus, usually droplets expressed from the oral, nasal, or [pharyngeal](/wiki/Pharynx) [mucosa](/wiki/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](/wiki/Bodily_fluid) or contaminated objects ([fomites](/wiki/Fomite)) 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.<ref name= FactSheet/> The virus can cross the [placenta](/wiki/Placenta), but the incidence of [congenital](/wiki/Congenital) smallpox is relatively low.<ref name=AFIP/> Smallpox is not notably infectious in the [prodromal](/wiki/Prodrome) period and viral shedding is usually delayed until the appearance of the rash, which is often accompanied by [lesions](/wiki/Lesion) 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.<ref name= PinkBook/> 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.[[15]](#cite_note-15) 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](/wiki/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.<ref name= PinkBook/> Age distribution of smallpox infections depends on [acquired immunity](/wiki/Acquired_immunity). [Vaccination](/wiki/Vaccination) [immunity](/wiki/Immunity_(medical)) declines over time and is probably lost within thirty years.<ref name=AFIP/> Smallpox is not known to be transmitted by insects or animals and there is no [asymptomatic carrier](/wiki/Asymptomatic_carrier) state.<ref name= PinkBook/>

## Diagnosis[[edit](/index.php?title=(none)&action=edit&section=10)]

The clinical definition of smallpox is an illness with acute onset of fever equal to or greater than [Template:Convert](/wiki/Template:Convert) followed by a rash characterized by firm, deep seated vesicles or pustules in the same stage of development without other apparent cause.<ref name= PinkBook/> If a clinical case is observed, smallpox is confirmed using laboratory tests.

[Microscopically](/wiki/Microscope), poxviruses produce characteristic [cytoplasmic](/wiki/Cytoplasmic) inclusions, the most important of which are known as [Guarnieri bodies](/wiki/Guarnieri_bodies), and are the sites of [viral replication](/wiki/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.[[16]](#cite_note-16) The diagnosis of an orthopoxvirus infection can also be made rapidly by [electron microscopic](/wiki/Electron_microscopy) examination of pustular fluid or scabs. However, all orthopoxviruses exhibit identical brick-shaped [virions](/wiki/Virions) by electron microscopy.<ref name=AFIP/> However, if particles with the characteristic morphology of [herpesviruses](/wiki/Herpesvirus) are seen this will eliminate smallpox and other orthopoxvirus infections.

Definitive laboratory identification of variola virus involves growing the virus on [chorioallantoic membrane](/wiki/Chorioallantoic_membrane) (part of a chicken [embryo](/wiki/Embryo)) and examining the resulting pock lesions under defined temperature conditions.[[17]](#cite_note-17) Strains may be characterized by [polymerase chain reaction](/wiki/Polymerase_chain_reaction) (PCR) and [restriction fragment length polymorphism](/wiki/Restriction_fragment_length_polymorphism) (RFLP) analysis. [Serologic](/wiki/Serologic) tests and [enzyme linked immunosorbent assays](/wiki/Enzyme_linked_immunosorbent_assay) (ELISA), which measure variola virus-specific immunoglobulin and antigen have also been developed to assist in the diagnosis of infection.[[18]](#cite_note-18) [Chickenpox](/wiki/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.<ref name= PinkBook/>

<gallery widths="200px" heights="200px"> Image:Smallpox CAM.png|Smallpox virus lesions on the [chorioallantoic membrane](/wiki/Chorioallantoic_membrane) of a developing chick. Image:Smallpox\_versus\_chickenpox\_english\_plain.svg|In contrast to the rash in smallpox, the rash in [chickenpox](/wiki/Chickenpox) occurs mostly on the torso, spreading less to the limbs. File:Female smallpox patient -- late-stage confluent maculopapular scarring.jpg|An Italian female smallpox patient whose skin displayed the characteristics of late-stage confluent maculopapular scarring, 1965. </gallery>

## Prevention[[edit](/index.php?title=(none)&action=edit&section=11)]

[Template:Main](/wiki/Template:Main) [thumb|Components of a modern smallpox](/wiki/File:Smallpox_vaccine.jpg) [vaccination](/wiki/Vaccination) kit including the [diluent](/wiki/Diluent), a vial of Dryvax vaccinia vaccine, and a [bifurcated needle](/wiki/Bifurcated_needle). The earliest procedure used to prevent smallpox was [inoculation](/wiki/Inoculation) (known as variolation after the introduction of [smallpox vaccine](/wiki/Smallpox_vaccine) to avoid possible confusion), which likely occurred in India, Africa, and China well before the practice arrived in Europe.[[19]](#cite_note-19) However, the idea that inoculation originated in India has been challenged, as few of the ancient [Sanskrit](/wiki/Sanskrit) medical texts described the process of inoculation.[[20]](#cite_note-20) 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](/wiki/Ming_dynasty).<ref name= Temple>Temple, Robert. (1986). *The Genius of China: 3,000 Years of Science, Discovery, and Invention*. With a forward by Joseph Needham. New York: Simon and Schuster, Inc. ISBN 0-671-62028-2. p. 135–37.</ref> If successful, inoculation produced lasting [immunity](/wiki/Immunity_(medical)) 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.<ref name= PinkBook/>

[Lady Mary Wortley Montagu](/wiki/Lady_Mary_Wortley_Montagu) observed smallpox inoculation during her stay in the [Ottoman Empire](/wiki/Ottoman_Empire), writing detailed accounts of the practice in her letters, and enthusiastically promoted the procedure in England upon her return in 1718.[[21]](#cite_note-21) In 1721, [Cotton Mather](/wiki/Cotton_Mather#Smallpox_inoculation_controversy) and colleagues provoked controversy in Boston by inoculating hundreds. In 1796, [Edward Jenner](/wiki/Edward_Jenner), a doctor in [Berkeley, Gloucestershire](/wiki/Berkeley,_Gloucestershire), rural England, discovered that immunity to smallpox could be produced by inoculating a person with material from a [cowpox](/wiki/Cowpox) lesion. Cowpox is a poxvirus in the same family as variola. Jenner called the material used for inoculation [vaccine](/wiki/Vaccine), from the [root word](/wiki/Root_(linguistics)) *vacca*, which is [Latin](/wiki/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](/wiki/Vaccinia) virus. Vaccinia is in the same family as cowpox and variola, but is [genetically](/wiki/Genetics) distinct from both. The origin of vaccinia virus and how it came to be in the vaccine are not known.<ref name= PinkBook/>

[thumb|left|An 1802 cartoon of the early controversy surrounding](/wiki/File:The_cow_pock.jpg) [Edward Jenner's](/wiki/Edward_Jenner) vaccination theory, showing using his [cowpox](/wiki/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.[[22]](#cite_note-22) The [antibodies](/wiki/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.<ref name= CDCvac/> 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.[[23]](#cite_note-23) [thumb|A demonstration by medical personnel on use of a bifurcated needle to deliver the smallpox vaccine, 2002.](/wiki/File:Smallpox_vaccine_injection.jpg) 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](/wiki/Allergic_reaction) at the site of the vaccination ([erythema multiforme](/wiki/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](/wiki/Encephalitis) or severe [necrosis](/wiki/Necrosis) in the area of vaccination (called progressive vaccinia).<ref name= CDCvac/>

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.<ref name=WHO\_Factsheet/>[[24]](#cite_note-24) 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[[25]](#cite_note-25)). By 1986, routine vaccination had ceased in all countries.<ref name=WHO\_Factsheet/> It is now primarily recommended for laboratory workers at risk for occupational exposure.<ref name= PinkBook/>

## Treatment[[edit](/index.php?title=(none)&action=edit&section=12)]

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.<ref name=CDCvac>[Template:Cite web](/wiki/Template:Cite_web)</ref> Other than vaccination, treatment of smallpox is primarily supportive, such as wound care and infection control, fluid therapy, and possible [ventilator](/wiki/Ventilator) assistance. Flat and hemorrhagic types of smallpox are treated with the same therapies used to treat [shock](/wiki/Shock_(circulatory)), such as [fluid resuscitation](/wiki/Fluid_replacement). People with semi-confluent and confluent types of smallpox may have therapeutic issues similar to patients with extensive skin [burns](/wiki/Burn).<ref name= Fenner4/>

No drug is currently approved for the treatment of smallpox. However, [antiviral](/wiki/Antiviral_drug) treatments have improved since the last large smallpox epidemics, and studies suggest that the antiviral drug [cidofovir](/wiki/Cidofovir) might be useful as a therapeutic agent. The drug must be administered [intravenously](/wiki/Intravenously), however, and may cause serious [kidney](/wiki/Renal) toxicity.[[26]](#cite_note-26)

## Prognosis[[edit](/index.php?title=(none)&action=edit&section=13)]

[thumb|upright|A case of smallpox, 1886](/wiki/File:Variola_1.jpg) 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.<ref name=training1/> There is no evidence of chronic or recurrent infection with variola virus.<ref name=training1/>

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](/wiki/Immune_complex), overwhelming [viremia](/wiki/Viremia), or an uncontrolled [immune response](/wiki/Immune_response) may be contributing factors.<ref name=PinkBook/> In early hemorrhagic smallpox, death occurs suddenly about six days after the fever develops. Cause of death in hemorrhagic cases involved [heart failure](/wiki/Heart_failure), sometimes accompanied by [pulmonary edema](/wiki/Pulmonary_edema). In late hemorrhagic cases, high and sustained viremia, severe [platelet](/wiki/Platelet) loss and poor immune response were often cited as causes of death.<ref name= Fenner1/> In flat smallpox modes of death are similar to those in burns, with loss of fluid, protein and [electrolytes](/wiki/Electrolyte) beyond the capacity of the body to replace or acquire, and fulminating [sepsis](/wiki/Sepsis).<ref name= Fenner4>[Template:Cite book](/wiki/Template:Cite_book)</ref>

### Complications[[edit](/index.php?title=(none)&action=edit&section=14)]

Complications of smallpox arise most commonly in the [respiratory system](/wiki/Respiratory_system) and range from simple [bronchitis](/wiki/Bronchitis) to fatal [pneumonia](/wiki/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](/wiki/Bacteria) infection of the skin is a relatively uncommon complication of smallpox. When this occurs, the fever usually remains elevated.<ref name=PinkBook/>

Other complications include [encephalitis](/wiki/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](/wiki/Conjunctiva), and [cornea](/wiki/Cornea), leading to complications such as [conjunctivitis](/wiki/Conjunctivitis), [keratitis](/wiki/Keratitis), [corneal ulcer](/wiki/Corneal_ulcer), [iritis](/wiki/Iritis), [iridocyclitis](/wiki/Iridocyclitis), and optic [atrophy](/wiki/Atrophy). [Blindness](/wiki/Blindness) results in approximately 35 percent to 40 percent of eyes affected with keratitis and corneal ulcer. Hemorrhagic smallpox can cause subconjunctival and [retinal](/wiki/Retina) hemorrhages. In 2 to 5 percent of young children with smallpox, virions reach the joints and bone, causing [*osteomyelitis*](/wiki/Osteomyelitis) *variolosa*. Lesions are symmetrical, most common in the elbows, [tibia](/wiki/Tibia), and [fibula](/wiki/Fibula), and characteristically cause separation of an [epiphysis](/wiki/Epiphysis) and marked [periosteal](/wiki/Periosteum) reactions. Swollen joints limit movement, and [arthritis](/wiki/Arthritis) may lead to limb deformities, [ankylosis](/wiki/Ankylosis), malformed bones, flail joints, and stubby fingers.<ref name=AFIP/>

## History[[edit](/index.php?title=(none)&action=edit&section=15)]

[Template:Main](/wiki/Template:Main)

### Disease emergence[[edit](/index.php?title=(none)&action=edit&section=16)]

[thumb|upright|Statue of](/wiki/File:Sopona.jpg) [Sopona](/wiki/Sopona), the [Yoruba](/wiki/Yoruba_religion) god thought to cause the disease.

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),<ref name=Shchelkunov2011>[Template:Cite journal](/wiki/Template:Cite_journal)</ref>[[27]](#cite_note-27) [Egyptian](/wiki/Ancient_Egypt) [mummy](/wiki/Mummy) of [Ramses V](/wiki/Ramses_V) who died more than 3000 years ago (1145 BC)<ref name=Ramses/> and China (1122 BC).<ref name=Hopkins\_2002>[Template:Cite book](/wiki/Template:Cite_book) Originally published as *Princes and Peasants: Smallpox in History* (1983), ISBN 0-226-35177-7</ref> 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.<ref name= Fenner1/> In Japan, the epidemic of 735–737 is believed to have killed as much as one-third of the population.<ref name=Hays/>[[28]](#cite_note-28) At least seven religious deities have been specifically dedicated to smallpox, such as the god [Sopona](/wiki/Sopona) in the [Yoruba religion](/wiki/Yoruba_religion). In India, the Hindu goddess of smallpox, [Sitala Mata](/wiki/Shitala_Devi), was worshiped in temples throughout the country.[[29]](#cite_note-29) [thumb|left|Drawing accompanying text in Book XII of the 16th-century](/wiki/File:FlorentineCodex_BK12_F54_smallpox.jpg) [*Florentine Codex*](/wiki/Florentine_Codex) (compiled 1540–1585), showing [Nahuas](/wiki/Nahua_peoples) of conquest-era central Mexico with smallpox.

The timing of the arrival of smallpox in Europe and south-western Asia is less clear. Smallpox is not clearly described in either the [Old](/wiki/Old_Testament) or [New Testaments](/wiki/New_Testament) of the Bible or in the literature of the Greeks or Romans. While some have identified the [Plague of Athens](/wiki/Plague_of_Athens)—which was said to have originated in "[Ethiopia](/wiki/Aethiopia_(Classical_Greek_term))" and Egypt—or the plague that lifted Carthage's 396 BC [siege of Syracuse](/wiki/Siege_of_Syracuse_(397_BC)) with smallpox,<ref name=SmaPoHist/> many scholars agree it is very unlikely such a serious disease as variola major would have escaped being described by [Hippocrates](/wiki/Hippocrates) if it had existed in the Mediterranean region during his lifetime.[[30]](#cite_note-30) While the [Antonine Plague](/wiki/Antonine_Plague) that swept through the [Roman Empire](/wiki/Roman_Empire) in AD 165[Template:Ndash](/wiki/Template:Ndash)180 may have been caused by smallpox,[[31]](#cite_note-31) Saint [Nicasius of Rheims](/wiki/Nicasius_of_Rheims) became the patron saint of smallpox victims for having supposedly survived a bout in 450,<ref name=SmaPoHist>"[The History of Smallpox and Its Spread around the World](http://whqlibdoc.who.int/smallpox/9241561106_chp5.pdf)". Accessed 28 January 2013.</ref> and Saint [Gregory of Tours](/wiki/Gregory_of_Tours) recorded a similar outbreak in France and Italy in 580, the first use of the term *variola*;<ref name=SmaPoHist/> other historians speculate that [Arab](/wiki/Arab) armies first carried smallpox from Africa into Southwestern Europe during the 7th and 8th centuries.<ref name= Fenner1/> In the 9th century the [Persian physician](/wiki/Islamic_medicine), [Rhazes](/wiki/Muhammad_ibn_Zakariya_ar-Razi), provided one of the most definitive descriptions of smallpox and was the first to differentiate smallpox from [measles](/wiki/Measles) and [chickenpox](/wiki/Chickenpox) in his *Kitab fi al-jadari wa-al-hasbah* (*The Book of Smallpox and Measles*).[[32]](#cite_note-32) During the [Middle Ages](/wiki/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](/wiki/Crusades). By the 16th century smallpox had become well established across most of Europe.<ref name= Fenner1/> 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.<ref name= Fenner1/>

[thumb|upright|A smallpox sufferer in the United States, 1912](/wiki/File:SmallpoxvictimIllinois1912.jpg)

There are no credible descriptions of smallpox-like disease in the [Americas](/wiki/Americas) before the westward exploration by Europeans in the 15th century AD.<ref name=Li2007/> Smallpox was introduced into the Caribbean island of [Hispaniola](/wiki/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](/wiki/Amerindian) population and was an important factor in the conquest of the [Aztecs](/wiki/Aztec) and the [Incas](/wiki/Inca) by the Spaniards.<ref name= Fenner1/> Settlement of the east coast of North America in 1633 in [Plymouth, Massachusetts](/wiki/Plymouth,_Massachusetts) was also accompanied by devastating outbreaks of smallpox among Native American populations,[[33]](#cite_note-33) and subsequently among the native-born colonists.[[34]](#cite_note-34) Case fatality rates during outbreaks in Native American populations were as high as 80–90%.[[35]](#cite_note-35) Smallpox was introduced into [Australia](/wiki/Australia) in 1789 and again in 1829.<ref name= Fenner1/> Although the disease was never endemic on the continent,<ref name= Fenner1/> it was the principal cause of death in [Aboriginal](/wiki/Indigenous_Australians) populations between 1780 and 1870.[[36]](#cite_note-36) By the mid-18th century smallpox was a major [endemic disease](/wiki/Endemic_(epidemiology)) 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.[[37]](#cite_note-37) Up to 10 percent of [Swedish](/wiki/Sweden) infants died of smallpox each year,<ref name=Hays/> and the death rate of infants in [Russia](/wiki/Russia) may have been even higher.<ref name=Hopkins\_2002/> The widespread use of [variolation](/wiki/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](/wiki/Walk) 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.<ref name= Fenner1/>

### Eradication[[edit](/index.php?title=(none)&action=edit&section=17)]

[Template:See also](/wiki/Template:See_also) [thumb|upright|Vaccination during the Smallpox Eradication and Measles Control Program in](/wiki/File:Fighting_smallpox_in_Niger,_1969.jpg) [Niger](/wiki/Niger), February 1969.

The English physician [Edward Jenner](/wiki/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](/wiki/Trinity,_Newfoundland_and_Labrador) in 1800 by [Dr. John Clinch](/wiki/John_Clinch), boyhood friend and medical colleague of Jenner.[[38]](#cite_note-38) As early as 1803, the Spanish Crown organized the [Balmis expedition](/wiki/Balmis_expedition) to transport the vaccine to the [Spanish colonies](/wiki/Spanish_Empire) in the Americas and the Philippines, and establish mass vaccination programs there.[[39]](#cite_note-39) The [U.S. Congress](/wiki/United_States_Congress) passed the [Vaccine Act of 1813](/wiki/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](/wiki/Dutch_East_Indies).[[40]](#cite_note-40) In [British India](/wiki/British_India) a program was launched to propagate smallpox vaccination, through Indian vaccinators, under the supervision of European officials.[[41]](#cite_note-41) 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.[[42]](#cite_note-42) By 1832, the federal government of the United States established a smallpox vaccination program for [Native Americans](/wiki/Native_Americans_in_the_United_States).[[43]](#cite_note-43) In 1842, the United Kingdom banned inoculation, later progressing to [mandatory vaccination](/wiki/Vaccination_Act). The British government introduced compulsory smallpox vaccination by an Act of Parliament in 1853.[[44]](#cite_note-44) In the United States, from 1843 to 1855 first Massachusetts, and then other states required smallpox vaccination. Although some disliked these measures,[[45]](#cite_note-45) 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.[[46]](#cite_note-46) 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.<ref name=Plotkin\_1999>[Template:Cite book](/wiki/Template:Cite_book)</ref>

[thumb|left|Smallpox quarantine order, California, c. 1910](/wiki/File:Smallpox_keep_out_of_this_house..JPG)

The first [hemisphere](/wiki/Western_Hemisphere)-wide effort to eradicate smallpox was made in 1950 by the [Pan American Health Organization](/wiki/Pan_American_Health_Organization).[[47]](#cite_note-47) The campaign was successful in eliminating smallpox from all American countries except Argentina, Brazil, Colombia, and Ecuador.<ref name=Plotkin\_1999/> In 1958 Professor [Viktor Zhdanov](/wiki/Viktor_Zhdanov), Deputy Minister of Health for the [USSR](/wiki/Soviet_Union), called on the [World Health Assembly](/wiki/World_Health_Assembly) to undertake a global initiative to [eradicate](/wiki/Eradication_of_infectious_diseases) smallpox.<ref name= Fenner2/> The proposal (Resolution WHA11.54) was accepted in 1959.<ref name= Fenner2>[Template:Cite book](/wiki/Template:Cite_book)</ref> 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](/wiki/Indian_subcontinent). In 1966 an international team, the Smallpox Eradication Unit, was formed under the leadership of an American, [Donald Henderson](/wiki/Donald_Henderson).<ref name= Fenner3>[Template:Cite book](/wiki/Template:Cite_book)</ref> 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](/wiki/Disease_surveillance) method promoted by Czech epidemiologist [Karel Raška](/wiki/Karel_Raška).[[48]](#cite_note-48)[[49]](#cite_note-49) [thumb|upright|Two-year-old](/wiki/File:Rahima_Banu.jpg) [Rahima Banu](/wiki/Rahima_Banu) of Bangladesh (pictured) was the last person infected with naturally occurring *Variola major*, in 1975 In the early 1950s an estimated 50 million cases of smallpox occurred in the world each year.<ref name=WHO\_Factsheet/> 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](/wiki/Asymptomatic_carrier) 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.<ref name=Plotkin\_1999/>

The last major European outbreak of smallpox was in [1972 in Yugoslavia](/wiki/1972_outbreak_of_smallpox_in_Yugoslavia), after a pilgrim from [Kosovo](/wiki/Kosovo) returned from the Middle East, where he had contracted the virus. The epidemic infected 175 people, causing 35 deaths. Authorities declared [martial law](/wiki/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.[[50]](#cite_note-50) Prior to this, there had been a smallpox outbreak in May–July 1963 in [Stockholm](/wiki/Stockholm), Sweden, brought from the [Far East](/wiki/Far_East) by a Swedish sailor; this had been dealt with by quarantine measures and vaccination of the local population.[[51]](#cite_note-51) By the end of 1975, smallpox persisted only in the [Horn of Africa](/wiki/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](/wiki/Frank_Fenner). As the campaign neared its goal, Fenner and his team played an important role in verifying eradication.[[52]](#cite_note-52) The last naturally occurring case of indigenous smallpox (*Variola minor*) was diagnosed in [Ali Maow Maalin](/wiki/Ali_Maow_Maalin), a hospital cook in Merca, [Somalia](/wiki/Somalia), on 26 October 1977.<ref name= PinkBook/> The last naturally occurring case of the more deadly *Variola major* had been detected in October 1975 in a two-year-old [Bangladeshi](/wiki/Bangladesh) girl, [Rahima Banu](/wiki/Rahima_Banu).<ref name=PrestonNY>[Template:Cite news](/wiki/Template:Cite_news)</ref>

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.[[53]](#cite_note-53) The first two sentences of the resolution read:

[Template:Quote](/wiki/Template:Quote)

### Post-eradication[[edit](/index.php?title=(none)&action=edit&section=18)]

[Template:Further](/wiki/Template:Further) [thumb|Three former directors of the Global Smallpox Eradication Program read the news that smallpox had been globally eradicated, 1980](/wiki/File:Directors_of_Global_Smallpox_Eradication_Program.jpg) The last cases of smallpox in the world occurred in an outbreak of two cases (one of which was fatal) in [Birmingham](/wiki/Birmingham), [UK](/wiki/United_Kingdom) in 1978. A medical photographer, [Janet Parker](/wiki/Janet_Parker), contracted the disease at the [University of Birmingham Medical School](/wiki/University_of_Birmingham_Medical_School) and died on September 11, 1978,<ref name= Pennington>[Template:Cite journal](/wiki/Template:Cite_journal)</ref> after which Professor Henry Bedson, the scientist responsible for smallpox research at the university, committed suicide.<ref name=Barquet/>[[54]](#cite_note-54) All known stocks of smallpox were subsequently destroyed or transferred to two WHO-designated reference laboratories with [BSL-4](/wiki/BSL-4) facilities—the United States' [Centers for Disease Control and Prevention](/wiki/Centers_for_Disease_Control_and_Prevention) and Russia's [State Research Center of Virology and Biotechnology VECTOR](/wiki/State_Research_Center_of_Virology_and_Biotechnology_VECTOR).[[55]](#cite_note-55) 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.[[56]](#cite_note-56) 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.[[57]](#cite_note-57) Destroying existing stocks would reduce the risk involved with ongoing smallpox research; the stocks are not needed to respond to a smallpox outbreak.[[58]](#cite_note-58) Some scientists have argued that the stocks may be useful in developing new vaccines, antiviral drugs, and diagnostic tests;[[59]](#cite_note-59) 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.<ref name=AGIES>[Comments on the Scientific Review of Variola Virus Research, 1999‐2010.](http://www.who.int/entity/csr/resources/publications/WHO_HSE_GAR_BDP_2010_4/en/index.html) Advisory Group of Independent Experts to review the smallpox research program (AGIES) WHO document WHO/HSE/GAR/BDP/2010.4</ref> The latter view is frequently supported in the scientific community, particularly among veterans of the WHO Smallpox Eradication Program.<ref name=eradedit>[Template:Cite journal](/wiki/Template:Cite_journal)</ref>

In March 2004 smallpox [scabs](/wiki/Coagulation) were found tucked inside an envelope in a book on [Civil War](/wiki/American_Civil_War) medicine in [Santa Fe, New Mexico](/wiki/Santa_Fe,_New_Mexico).<ref name=USA\_Today\_20031226>[Template:Cite news](/wiki/Template:Cite_news)</ref> The envelope was labeled as containing scabs from a vaccination and gave scientists at the [Centers for Disease Control and Prevention](/wiki/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](/wiki/National_Institutes_of_Health) location in [Bethesda, Maryland](/wiki/Bethesda,_Maryland).[[60]](#cite_note-60)

## Society and culture[[edit](/index.php?title=(none)&action=edit&section=19)]

### Biological warfare[[edit](/index.php?title=(none)&action=edit&section=20)]

The British used smallpox as a [biological warfare](/wiki/Biological_warfare) agent at the [Siege of Fort Pitt](/wiki/Pontiac's_War#Siege_of_Fort_Pitt) during the [French and Indian Wars](/wiki/French_and_Indian_Wars) (1754–1763) against France and its [Native American](/wiki/Indigenous_peoples_of_the_Americas) allies.[[61]](#cite_note-61)[[62]](#cite_note-62) 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 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".[[63]](#cite_note-63) 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."[[64]](#cite_note-64)[[65]](#cite_note-65) 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](/wiki/American_Revolutionary_War) (1775–1783).[[66]](#cite_note-66)[[67]](#cite_note-67) 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](/wiki/New_South_Wales).[[68]](#cite_note-68) 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.<ref name= CDCcourse>[History and Epidemiology of Global Smallpox Eradication](http://www.bt.cdc.gov/agent/smallpox/training/overview/pdf/eradicationhistory.pdf) From the training course titled "Smallpox: Disease, Prevention, and Intervention". The CDC and the [World Health Organization](/wiki/World_Health_Organization). Slide 16–17.</ref> Specific allegations made against Iraq in this respect, however, proved to be mistaken.<ref name= USfalseallegation>Burkeman, Oliver (19 September 2003). ["No evidence of smallpox"](http://www.guardian.co.uk/world/2003/sep/20/iraq.oliverburkeman). [*The Guardian*](/wiki/The_Guardian). Accessed 10 May 2012.</ref>

Concern has been expressed by some that [artificial gene synthesis](/wiki/Artificial_gene_synthesis) could be used to recreate the virus from existing digital genomes, for use in biological warfare.<ref name=sunshine/> Insertion of the synthesized smallpox DNA into existing related [pox viruses](/wiki/Pox_virus) could theoretically be used to recreate the virus.<ref name=sunshine>[The Genetic Engineering of Smallpox. WHO’s Retreat from the Eradication of Smallpox Virus and Why it Should be Stopped](http://www.biosafety-info.net/file_dir/413148854af122567.pdf) A BRIEFING PAPER BY THE SUNSHINE PROJECT. 2002.</ref> 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.<ref name= Synbiorisk>[Smallpox Virus Stocks at the 64th WHA – Implementing the Conclusions of the Major Review](http://www.smallpoxbiosafety.org/papers/WHAvariola2011.pdf) Third World Network, Briefing Paper by Edward Hammond, page 8.</ref>

### Notable cases[[edit](/index.php?title=(none)&action=edit&section=21)]

[thumb|In 1767, the 11-year-old composer](/wiki/File:Martini_bologna_mozart_1777.jpg) [Wolfgang Amadeus Mozart](/wiki/Wolfgang_Amadeus_Mozart) survived a smallpox outbreak in [Austria](/wiki/Austria) that killed Holy Roman Empress [Maria Josepha](/wiki/Maria_Josepha_of_Bavaria), who became the second consecutive wife of [Holy Roman Emperor Joseph II](/wiki/Joseph_II,_Holy_Roman_Emperor) to die of the disease, as well as [Archduchess Maria Josepha](/wiki/Archduchess_Maria_Josepha_of_Austria). (See [Mozart and smallpox](/wiki/Mozart_and_smallpox).)

Famous historical figures who contracted smallpox include Lakota Chief [Sitting Bull](/wiki/Sitting_Bull), [Ramses V](/wiki/Ramses_V) of [Egypt](/wiki/Egypt),[[76]](#cite_note-76) the [Kangxi Emperor](/wiki/Kangxi_Emperor) (survived), [Shunzhi Emperor](/wiki/Shunzhi_Emperor) and [Tongzhi Emperor](/wiki/Tongzhi_Emperor) (refer to the official history) of China, [Date Masamune](/wiki/Date_Masamune) of Japan (who lost an eye to the disease). [Cuitláhuac](/wiki/Cuitláhuac), the 10th [tlatoani](/wiki/Tlatoani) (ruler) of the [Aztec](/wiki/Aztec) city of [Tenochtitlan](/wiki/Tenochtitlan), died of smallpox in 1520, shortly after its introduction to the [Americas](/wiki/Americas), and the Incan emperor [Huayna Capac](/wiki/Huayna_Capac) died of it in 1527. More recent public figures include [Guru Har Krishan](/wiki/Guru_Har_Krishan), 8th Guru of the Sikhs, in 1664, [Peter II of Russia](/wiki/Peter_II_of_Russia) in 1730 (died),[[77]](#cite_note-77) [George Washington](/wiki/George_Washington) (survived), king [Louis XV](/wiki/Louis_XV) in 1774 (died) and [Maximilian III Joseph, Elector of Bavaria](/wiki/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](/wiki/Henry_VIII_of_England) survived the disease but were scarred by it. These include his sister [Margaret, Queen of Scotland](/wiki/Margaret_Tudor), his fourth wife, [Anne of Cleves](/wiki/Anne_of_Cleves), and his two daughters: [Mary I of England](/wiki/Mary_I_of_England) in 1527 and [Elizabeth I of England](/wiki/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](/wiki/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](/wiki/Henry_VIII_of_England), [Edward VI](/wiki/Edward_VI_of_England), 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 both women, who had both had it and survived). [Louis XV of France](/wiki/Louis_XV_of_France) succeeded his great-grandfather [Louis XIV](/wiki/Louis_XIV) through a series of deaths of smallpox or measles among those earlier in the succession line. He himself died of the disease in 1774. [William III](/wiki/William_III_of_England) lost his mother to the disease when he was only ten years old in 1660, and named his uncle [Charles](/wiki/Charles_II_of_England) as legal guardian: her death from smallpox would indirectly spark a chain of events that would eventually lead to the permanent ousting of the Stuart line from the British throne. William III's wife, [Mary II of England](/wiki/Mary_II_of_England), died from smallpox as well.

In Russia, [Peter II of Russia](/wiki/Peter_II_of_Russia) died of the disease at 15 years of age. Also, prior to becoming [Russian Emperor](/wiki/Russian_Empire), [Peter III](/wiki/Peter_III_of_Russia) caught the virus and suffered greatly from it. He was left scarred and disfigured. His wife, [Catherine the Great](/wiki/Catherine_the_Great), was spared but fear of the virus clearly had its effects on her. She feared for her son and heir [Pavel's](/wiki/Paul_I_of_Russia) safety so much that she made sure that large crowds were kept at bay and sought to isolate him. Eventually, she decided to have herself inoculated by a [Scottish](/wiki/Scotland) doctor, [Thomas Dimsdale](/wiki/Thomas_Dimsdale). While this was considered a controversial method at the time, she succeeded. Her son Pavel was later inoculated as well. Catherine then sought to have inoculations throughout her empire stating: "My objective was, through my example, to save from death the multitude of my subjects who, not knowing the value of this technique, and frightened of it, were left in danger." By 1800, approximately 2 million inoculations were administered in the Russian Empire.[[78]](#cite_note-78) In China, the [Qing Dynasty](/wiki/Qing_Dynasty) had extensive protocols to protect [Manchus](/wiki/Manchu) from [Peking's](/wiki/Peking) endemic smallpox.

U.S. Presidents [George Washington](/wiki/George_Washington), [Andrew Jackson](/wiki/Andrew_Jackson), and [Abraham Lincoln](/wiki/Abraham_Lincoln) all contracted and recovered from the disease. Washington became infected with smallpox on a visit to [Barbados](/wiki/Barbados) in 1751.[[79]](#cite_note-79) Jackson developed the illness after being taken prisoner by the British during the American Revolution, and though he recovered, his brother Robert did not.[[79]](#cite_note-79) Lincoln contracted the disease during his Presidency, possibly from his son Tad, and was quarantined shortly after giving the Gettysburg address in 1863.[[79]](#cite_note-79) Famous theologian [Jonathan Edwards](/wiki/Jonathan_Edwards_(theologian)) died of smallpox in 1758 following an inoculation.[[80]](#cite_note-80) [Soviet](/wiki/Soviet_Union) leader [Joseph Stalin](/wiki/Joseph_Stalin) fell ill with smallpox at the age of seven. His face was badly scarred by the disease. He later had photographs retouched to make his pockmarks less apparent.[[81]](#cite_note-81) Hungarian poet [Ferenc Kölcsey](/wiki/Ferenc_Kölcsey), who wrote the Hungarian national anthem, lost his right eye to smallpox.[[82]](#cite_note-82)

### Tradition and religion[[edit](/index.php?title=(none)&action=edit&section=22)]

[thumb|The Hindu goddess](/wiki/File:Kalighat_Shitala.jpg) [Shitala](/wiki/Shitala) was worshipped to prevent or cure smallpox. In the face of the devastation of smallpox, various smallpox gods and goddesses have been worshipped throughout parts of the [Old World](/wiki/Old_World), for example in China and in India. In China, the smallpox goddess was referred to as T’ou-Shen Niang-Niang.[[83]](#cite_note-83) 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](/wiki/Euphemism) intended to avert offending the goddess, for example.[[84]](#cite_note-84) 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.[[84]](#cite_note-84) 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.[[83]](#cite_note-83) 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.[[84]](#cite_note-84) India, like China, created a goddess in response to its exposure to smallpox. The Hindu goddess [Shitala](/wiki/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.[[85]](#cite_note-85) 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.[[84]](#cite_note-84) 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.[[86]](#cite_note-86) In cultures that did not recognize a smallpox deity, there was often nonetheless a belief in [smallpox demons](/wiki/Smallpox_demon), 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](/wiki/Charles_V_of_France) and [Elizabeth I of England](/wiki/Elizabeth_I_of_England).<ref name=SmaPoHist/> Afforded scientific credibility through the studies by Finsen showing that red light reduced scarring,<ref name=SmaPoHist/> this belief persisted even until the 1930s.

## See also[[edit](/index.php?title=(none)&action=edit&section=23)]

[Template:Portal](/wiki/Template:Portal)

* [1837 Great Plains smallpox epidemic](/wiki/1837_Great_Plains_smallpox_epidemic)
* [Aral smallpox incident](/wiki/Aral_smallpox_incident)
* [Biological warfare](/wiki/Biological_warfare)
* [CCR5-Δ32](/wiki/CCR5-Δ32)
* [Columbian Exchange](/wiki/Columbian_Exchange)
* [First Nations](/wiki/First_Nations)
* [Herd immunity](/wiki/Herd_immunity)
* [List of cutaneous conditions](/wiki/List_of_cutaneous_conditions)
* [List of epidemics](/wiki/List_of_epidemics)
* [Mathematics of mass vaccination](/wiki/Mathematical_modelling_in_epidemiology#Mathematics_of_mass_vaccination)
* [Pandemic](/wiki/Pandemic)
* [Population history of indigenous peoples of the Americas](/wiki/Population_history_of_indigenous_peoples_of_the_Americas)
* [*Smallpox 2002*](/wiki/Smallpox_2002)—film
* [Smallpox demon](/wiki/Smallpox_demon)
* [*What the Ancients Did for Us*](/wiki/What_the_Ancients_Did_for_Us)—a [BBC](/wiki/BBC) documentary highlighting ancient inoculation procedures in India

## References[[edit](/index.php?title=(none)&action=edit&section=24)]

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## Further reading[[edit](/index.php?title=(none)&action=edit&section=25)]

[Template:Refbegin](/wiki/Template:Refbegin)

* [Template:Cite book](/wiki/Template:Cite_book)
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* Lord Wharncliffe and W. Moy Thomas, editors. *The Letters and Works of Lady Mary Wortley Montagu, vol. 1,* London: Henry G. Bohn, 1861.

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## External links[[edit](/index.php?title=(none)&action=edit&section=26)]

[Template:Commons category](/wiki/Template:Commons_category)

* [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)
* [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), 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) 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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