

Smallpox

Variola major, Variola minor

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Etiology

Smallpox results from infection by variola virus (genus Orthopoxvirus, family Poxviridae). At least two strains of virus exist: the more virulent strain causes variola major and the less virulent strain causes variola minor.

The Orthopoxvirus genus also includes the vaccinia, monkeypox, cowpox, camelpox and ectromelia viruses; these agents resemble each other in electron micrographs and in many culture systems. They are also serologically cross-reactive. Monkeypox, which usually found in Africa, closely resembles smallpox; in monkeypox infections, the mortality rate is lower and the cervical and inguinal lymph nodes are highly enlarged.

Geographic Distribution

The last naturally acquired case of smallpox occurred in 1977 and the last two laboratory-acquired infections in 1978. In 1980, the World Health Organization (WHO) declared that endemic smallpox had been eradicated. Currently, the only known stocks of virus are stored at the Centers for Disease Control and Prevention (CDC) in Atlanta and the Institute for Viral Preparations in Moscow. Other countries may have clandestine stores of virus.

Transmission

The smallpox virus must be continuously transmitted from human to human to survive; humans do not become long-term carriers and animal reservoirs do not exist. Virus is spread by direct contact or inhalation of aerosols; infectious virus is present in oronasal secretions and in scabs from the skin. (The virus in scabs may be tightly bound and spread by this method may be less efficient.) Close contact is usually required for efficient virus transmission; therefore, smallpox mainly spreads to household members and others in close contact. Variola viruses can also be transmitted by individuals who maintain the virus in the throat without clinical signs. The potential for long-distance aerosol spread is controversial but has been demonstrated under certain conditions such as in hospitals. Transmission on fomites such as contaminated clothing or bedclothes is possible for short periods of time; however, variola does not remain viable for more than 2 days outside a human host. It is sensitive to heat and humidity; most natural epidemics occurred in the winter and spring.

Disinfection

Variola virus is susceptible to various disinfectants including 1% sodium hypochlorite, 0.1N sodium hydroxide, 1% peracetic acid, formaldehyde, ethylene oxide and others. The virus can also be destroyed by autoclaving or boiling for 10 minutes.

Infections in Humans

Incubation Period

The incubation period is 7 to 19 days; 12 to 14 days is average.

Clinical Signs

Smallpox has an acute onset; the initial clinical signs may include fever, malaise, rigors, vomiting, headache, backache and occasionally delirium. Some people develop an erythematous rash during this prodromal phase. The characteristic skin lesions usually appear 2 to 3 days later; the first signs are macules, which develop into papules and eventually pustular vesicles. These lesions are most common on the face and extremities and develop in synchronous "crops." Approximately 8 to 14 days after the first symptoms appeared, the pustules develop scabs and heal, leaving depressed, depigmented scars. Severe scarring may occur.

Two forms of smallpox may be seen. Variola minor is characterized by milder clinical signs, smaller skin lesions and a low mortality rate; variola major is characterized by more severe disease and scarring and a higher mortality rate.



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Approximately 5 to 10% of individuals develop flat-type or hemorrhagic variants of variola major. The hemorrhagic form is more common in pregnant women. Patients with this form have more severe initial symptoms, which are followed by generalized erythema and hemorrhages in the skin and mucosa. The initial symptoms are similar in the malignant or 'flat' form; in this form, confluent, flat nonpustular lesions develop and the epidermis often peels in survivors. The hemorrhagic and malignant forms are usually fatal.

Communicability

Yes. Patients are known to be infectious from the time the rash appears and remain infectious until the time the scabs have separated (approximately 7 to 10 days). Some sources recommend quarantine for all contacts for 17 days post-exposure.

Diagnostic Tests

Smallpox is usually diagnosed by finding the characteristic viruses in skin scrapings examined by electron microscopy. Aggregations of virus particles called Guarnieri bodies are found under the light microscope. Gispén's modified silver stain can demonstrate Guarnieri bodies in vesicular scrapings; this test is rapid but relatively insensitive.

Differentiation of variola from vaccinia, monkeypox or cowpox requires virus isolation and identification. Variola, vaccinia, monkeypox and cowpox viruses look similar in most cell culture systems but can be distinguished by their characteristic lesions on the chorio-allantoic membranes of 10 to 12 day old chick embryos. Other biological tests are occasionally necessary for confirmation. A new polymerase chain reaction technique is expected to be an easier and more accurate method to identify closely related viruses as well as viral strains. In a confirmed outbreak, most cases are diagnosed clinically.

During recovery, patients develop high titers of hemagglutinin-inhibiting, neutralizing and complement fixing antibodies; antibodies to related viruses can be identified by cross-absorption studies.

Treatment and Vaccination

No effective treatment other than supportive therapy is known; cidofovir and other antiviral agents are under investigation.

An effective human vaccine is available and appears to be protective for at least 3 years. Vaccination after exposure can prevent disease or reduce clinical signs and the risk of death; vaccination is most effective if it is given within a few days after exposure. Vaccinia Immune Globulin (VIG) may also be helpful in post-exposure prophylaxis. Vaccines are contraindicated in immunosuppressed persons, those infected with HIV, persons with eczema, and people with three or more cardiac risk fac-

tors. Rare vaccine complications may include generalized vaccinia, progressive vaccinia, and postvaccinal encephalitis (which has a 25% fatality rate).

Morbidity and Mortality

Natural smallpox infections spread slowly, with infections transmitted mainly to family members and other close personal contacts. Aerosolized virus in biological weapons would be expected to infect large numbers of individuals; younger people have no immunity against this disease and the resistance of those vaccinated more than 10 years ago is unknown.

Variola minor is a milder disease; the mortality rate is approximately 1% in unvaccinated persons. The overall mortality rate for variola major is 3% in vaccinated individuals and 30% in unvaccinated; mortality is generally higher with the Asian form than African form and in children under a year old. The malignant and hemorrhagic forms of variola major develop in approximately 5 to 10% of infected people. These forms are almost always fatal; the mortality rate in the malignant form is 95%.

In the past, serious vaccine complications occurred in approximately 100 per million primary vaccinations. The risk of complications is higher in people with eczema, HIV or other immunosuppressive diseases, pregnant women, and those receiving cancer chemotherapy or radiation. In the 2003 vaccination campaign of civilians and military personnel, it was discovered that people with three or more cardiac risk factors should defer the vaccine. Those risk factors include being a current smoker or tobacco user, having high blood pressure, high cholesterol or triglycerides, high blood sugar, and/or a heart condition before age 50 in a parent, brother or sister.

Infections in Animals

Humans are the only mammals that are naturally susceptible to infection. Recently, Peter Jahrling's group at the U.S. Army Medical Research Institute of Infectious Diseases (USAMRIID) was able to infect cynomolgus monkeys with variola virus. Monkeys were infected with extremely high doses by either injection alone or both injection and aerosols. All of the research animals became ill and 12 of 14 animals died. Virus was found in skin pustules. Details of this experiment have not been published.

Internet Resources

Centers for Disease Control and Prevention (CDC)
Smallpox Pages

<http://www.bt.cdc.gov/agent/smallpox/index.asp>

Medical Microbiology

<http://www.gsbs.utmb.edu/microbook>

Medical Treatment and Response to Suspected
Smallpox: Information for Health Care

Providers During Biologic Emergencies (New York City Department of Health Bureau of Communicable Disease)

<http://www.nyc.gov/html/doh/html/cd/smallmd.html>

“Smallpox and Vaccinia.” In *Vaccines*, 3rd edition

<http://www.ncbi.nlm.nih.gov/books/bv.fcgi?call=bv.View..ShowSection&rid=vacc.chapter.d1e2084>

The Merck Manual

<http://www.merck.com/pubs/mmanual/>

USAMRIID’s *Medical Management of Biological Casualties Handbook*

<http://www.vnh.org/BIOCASU/toc.html>

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Cardiac Deaths After a Mass Smallpox Vaccination Campaign— New York City, 1947 *CDC MMWR*