**Smallpox**

**Causative Organism**
- Variola virus. Member of the genus Orthopoxvirus, which includes vaccinia virus, monkeypox virus, and cowpox virus.
- Variola is known to exist in at least 2 strains: 1) variola major, and 2) variola minor

**Clinical Manifestations**
- Clinical forms:
  1. Variola major - the severe and most common form. Four types: 1) ordinary - most frequent type, >90% of cases; 2) modified – mild, occurs in previously vaccinated persons; 3) flat - rare, very severe, usually fatal; 4) hemorrhagic - rare, very severe, usually fatal.
  2. Variola minor - less common, much less severe form.
- Incubation Period:
  - For naturally-acquired smallpox: 10-14 days, range 7-17 days.
  - Animal studies suggest that unnaturally large numbers of inhaled poxviruses may result in a significantly shortened incubation period; possibly as short as 3-5 days.
- Prodromal period (duration of 2-4 days)
  - Abrupt onset of fever, 101³-104⁰F; chills; malaise; headache; muscle pain; backache; nausea/vomiting; prostration. Delirium has been reported in 15% of patients.
  - Person is usually too sick to carry on normal activities.
  - Approximately 10% of light-skinned patients exhibit an erythematous rash.
  - Not infectious until lesions develop in the mouth.
- Eruptive stage (duration of 3-4 weeks)
  1) Enanthem
     - Appears about 24 hours before the skin rash.
     - Begins with minute red spots on the tongue and oropharyngeal mucosa.
     - Lesions enlarge and quickly form small, painful ulcerations, discharging virus into the saliva.
  2) Exanthem
     - Appears 2-4 days after onset of fever and evolves as follows (stage, days after rash onset):
       - Macules, 0-1 days
       - Papules, 2-3 days
       - Vesicles, 3-5 days
       - Pustules, 6-12 days
       - Crusts, 13-20 days
       - All crusts separated, 21-28 days (leaving depressed, depigmented scars)
     - Additional detail:
       - The rash starts as macules, usually on the face; lesions then appear on the proximal extremities, spread to the distal extremities and trunk over the next week.
       - The vesicles often show umbilication; the pustules are raised, round, firm, and deeply embedded in the skin.
       - The lesions on any one part of the body are in the same stage of development, and are
more abundant on the face and extremities (centrifugal distribution).
- There are lesions on the palms and soles in >50% of cases.

**Outcome:**
- Overall case-fatality rate in the past for variola major was about 30% in unvaccinated persons, and about 3% in vaccinated individuals; for variola minor, it was about 1% in unvaccinated persons.
- If death occurs, it has usually been during the second week of clinical disease.
- The precise cause of death is not entirely understood, but has historically been attributed to toxemia, with high levels of circulating immune complexes.
- Historically, case-fatality rates have been higher in certain populations (e.g., Pacific Islanders, Native Americans), at extremes of age, during pregnancy (reported average was 65% for ordinary smallpox), and in people with immunodeficiencies.
- Smallpox during pregnancy has resulted in an increased incidence of spontaneous abortions.
- Acute complications have included viral keratitis or secondary ocular infection, encephalitis, and arthritis (up to 2% in children). Bronchopneumonia was seen in severely ill patients.
- Partially immune patients, especially those vaccinated several years before smallpox exposure, could develop less severe forms of disease. Some previously immune individuals or infants with maternal antibodies could develop a short-lived, febrile syndrome without rash upon exposure to variola.
- Long-term sequelae include blindness from corneal scarring, growth abnormalities in children, and disfiguring or even physically debilitating dermal scarring.
- Animal studies suggest that unnaturally large numbers of inhaled poxviruses may result in fulminant pulmonary disease with or without appearance of rash before death (the implications of these findings for human disease resulting from intentional smallpox virus aerosolization are unknown).

**Period of communicability:**
- Communicability can begin during the prodromal period, just prior to exanthem onset, when lesions in the mouth ulcerate, releasing virus into oral secretions.
- Patients are most infectious during the first 7-10 days after rash onset.
- Although variola concentrations in the throat, conjunctiva, and urine diminish with time, the virus can be readily recovered from scabs throughout convalescence. Thus the person remains potentially infectious until the last scab falls off (usually 3-4 weeks after rash onset).

**Diagnosis**
- A protocol for evaluating a person with an acute, generalized vesicular or pustular rash illness for smallpox has been developed by the Centers for Disease Control and Prevention (CDC), and is available at http://emergency.cdc.gov/agent/smallpox/diagnosis/pdf/poxalgorithm1-5-12.pdf.
- A case evaluation will be performed for patients with vesicular/pustular rash illness of unknown origin. Specimens found to be of LOW or MODERATE smallpox risk may be referred to MSPHL. Specimens that are found to be of HIGH smallpox risk should NOT be referred to MSPHL, but will be referred to CDC for testing (however, see the next bullet point).
- It is very important for medical providers and hospitals to contact the Missouri State Public Health Laboratory (MSPHL) at 800/392-0272 (24/7) prior to obtaining specimens. MSPHL staff will provide guidance, and facilitate transporting specimens to the Centers for Disease Control and Prevention (CDC) for specific variola testing. (Laboratory testing for variola in clinical specimens is currently done only by CDC.)
- Differential diagnosis for smallpox includes chickenpox, monkeypox, disseminated herpes zoster, and a number of other conditions that cause vesicular exanthems.
- Clinical specimens for variola testing can include scrapings of skin lesions, lesion fluid, crusts, blood, and pharyngeal swabs.
- Diagnosis of an Orthopoxvirus infection can be made rapidly by electron microscopic exam of pustular fluid or scabs. But electron microscopy is not capable of discriminating variola from other Orthopoxviruses.
- Differentiation of Orthopoxviruses is made by nucleic acid-based testing (e.g., polymerase chain reaction [PCR]), and by culture. PCR is a rapid and specific means of making a variola diagnosis. However, for
purposes of diagnosing variola, it is presently available only at CDC (and the U.S. Army Medical Research Institute of Infectious Diseases [USAMRIID]).

- Serologic tests can also assist in diagnosis of acute Orthopoxvirus infection.
- Extreme caution should be used in collecting, preparing for shipment, and transporting any material suspected of being contaminated with variola. Instructions may be found at http://www.bt.cdc.gov/agent/smallpox/response-plan/files/guide-d.pdf.
- In a confirmed smallpox outbreak, diagnosis of the disease would likely be based on the clinical picture.
- It might be difficult to recognize relatively mild cases of smallpox in persons with partial immunity, or extremely severe cases in patients without classical disease (i.e., without the typical signs and symptoms).

**Treatment**

- Treatment for smallpox mainly consists of general supportive measures:
  - Adequate fluid intake (difficult because of the enanthem) and nutrition.
  - Alleviation of pain and fever.
  - Keeping the skin lesions clean to prevent bacterial superinfection.
  - Management of secondary infections if they occur.
- No Food and Drug Administration (FDA)-approved antiviral treatments are available.
- Three drugs have demonstrated efficacy in Orthopoxvirus animal models, and have been used to treat disseminated vaccinia infection. If used during the response to a smallpox outbreak, they would have to be given under an investigational new drug (IND) application.
  - Cidofovir (a nucleotide analogue of cytosine) has shown some in-vitro and in-vivo (animal studies) activity against Orthopoxviruses, but its effectiveness for treating smallpox (or vaccine adverse reactions) is not known. It must be administered IV and can cause serious renal toxicity.
  - ST-246 (formerly SIGA-246) is active against multiple orthopoxviruses, including variola virus.
  - CMX001 (prodrug of cidofovir)

**Transmission**

- Means of transmission of variola virus
  - Inhalation of virus-containing large airborne droplets is by far the most common type of person-to-person transmission.
    - Droplets are expressed from the oral, nasal, or pharyngeal mucosa of the infected person during the period of infectiousness. These droplets are then directly deposited onto the nasal or oral mucosal membranes, or into the alveoli of the lungs, of the susceptible person.
    - Such transmission generally requires face-to-face contact of ≤2 meters (≤6.5 feet) as the droplets do not travel more than a few meters in the air before settling out onto the ground.
  - Indirect spread via inhalation of fine-particle aerosols can occur, but is much less common.
    - These fine-particle aerosols can travel in the air greater distances than droplets, so face-to-face contact is not required for transmission to occur.
    - This type of spread has usually occurred in hospital settings where more severe cases of smallpox or cases with a cough were admitted and not isolated to areas of the hospital that had air supply and ventilation systems separate from other areas.
  - Contact with material from pustules or crusted scabs (either through direct contact, or indirect contact through fomites such as laundry or bedding) has, in rare instances, resulted in transmission of variola.
- Increased person-to-person transmission is associated with: 1) exposure to cases with confluent rash or severe enanthem, 2) exposure to cases with severe bronchiolitis and cough, 3) low humidity, and 4) crowding.
- Household secondary attack rates have been about 50%-60%. According to one source, the average secondary attack rate of variola major in unvaccinated household contacts was 58.4%; it was 3.8% in vaccinated household contacts.
- During the 1960s and 1970s in Europe, when smallpox was imported during the December to April period of high transmission, as many as 10 to 20 second-generation cases were often infected from a single case.
**Infection Control**

- When evaluating a rash illness patient, it is very important to immediately institute appropriate infection control precautions. If a case or suspect case of smallpox is identified in, or admitted to, a health care facility, strict standard, contact, and airborne precautions must be followed. (An N95 respirator should continue to be worn by health care workers with confirmed vaccination status who perform either routine patient care or other procedures on smallpox patients. USAMRIID points out that weaponized smallpox strains encountered in the future may be genetically altered to render the current vaccine ineffective.)

- According to the *CDC Smallpox Response Plan and Guidelines*, it is expected that once a large outbreak of smallpox is confirmed, all confirmed or suspected smallpox patients will be isolated in a facility (a “Type C facility”) that has been designated solely for the isolation of such patients.

- Detailed information on infection control is available in the *CDC Smallpox Response Plan and Guidelines*.

**Smallpox (Vaccinia) Vaccines**

- Smallpox vaccines contain live vaccinia virus (*not* variola virus), and cannot cause smallpox.
  - Inoculation of vaccinia virus causes a localized virus infection that induces immunity, which provides cross-protection against variola virus.
  - Smallpox vaccination provides high level immunity for 3 to 5 years, and decreasing immunity thereafter. If a person is vaccinated again later, immunity lasts even longer.
  - Vaccination with a verified clinical “take” (vesicle with subsequent scar formation) within the past 3 years has been considered to render a person immune to smallpox.
  - Historically, smallpox vaccine has been effective in preventing smallpox infection in 95% of those vaccinated. In addition, the vaccine has been proven to prevent or substantially lessen infection when given within a few days of exposure (see below).

- **ACAM2000®**
  - Live-virus vaccine containing vaccinia virus. (It is a "second generation" smallpox vaccine derived from a clone of Dryvax®, purified, and produced using modern cell culture technology.)
  - It is the current licensed (FDA-approved) vaccine for smallpox (has replaced Dryvax®).
  - Administered by the percutaneous route (scarification) into the upper arm with 15 insertions of a two-pronged (bifurcated) needle.
  - Effectiveness appears similar to that of Dryvax®, and current data indicate a similar safety profile.
  - Contraindications: Individuals with severe immunodeficiency who are not expected to benefit from the vaccine should not receive ACAM2000®.
  - In persons vaccinated for the first time (primary vaccination), the expected response is the appearance of a papule at the vaccination site after 2-5 days. The papule becomes vesicular, then pustular, and reaches its maximum size at 8-10 days after vaccination. The pustule dries and forms a scab, which usually separates within 14-21 days, leaving a pitted scar.
- Following primary vaccination, formation of a major cutaneous reaction by day 6-8 is evidence of a successful take and acquisition of protective immunity.

- Successful vaccination in an individual previously exposed to vaccine is confirmed when a major cutaneous reaction is observed 6 to 8 days post-vaccination. However, any prior vaccination may modify (reduce) the cutaneous response upon revaccination such that the absence of a cutaneous response does not necessarily indicate vaccination failure.

- Immune response to the vaccine
  - Neutralizing antibodies against vaccinia develop in >95% of individuals following primary vaccination, rise rapidly (by day 15-20 after vaccination), and may be boosted on revaccination. Antibody titers are highly variable.
  - Titers may remain high for longer periods following two or more vaccinations than after a primary vaccination.
  - The level of the neutralizing antibody response following primary vaccination is generally in proportion to the intensity of the cutaneous reaction.
  - The level of neutralizing antibody that is required to protect against smallpox has not been clearly established, although some studies indicate that persons with antibody titers >1:32 are protected.
  - Cellular immune responses are also elicited by vaccination and may contribute to protection and immunological memory.

- Virus shedding from the vaccination site
  - Virus is shed from the vaccination site during the period starting with the development of a papule (day 2-5).
  - Shedding ceases when the scab separates and the lesion is re-epithelialized, about 14-21 days after vaccination.

- More information on ACAM2000® is available at [http://www.fda.gov/BiologicsBloodVaccines/Vaccines/ApprovedProducts/ucm094065.htm](http://www.fda.gov/BiologicsBloodVaccines/Vaccines/ApprovedProducts/ucm094065.htm).

- **Imvamune®**
  - The manufacturer (Bavarian Nordic) describes Imvamune® as follows:
    - It is a third generation vaccine derived from the parent strain Modified Vaccinia virus Ankara (MVA), which is a highly attenuated pox virus that has lost the capacity to replicate in human cells, hence solving the main safety issue of conventional vaccines.
    - It has been shown in clinical trials to be a well tolerated smallpox vaccine in healthy subjects and persons with contraindications to traditional smallpox vaccines.
    - In pre-clinical trials, IMVAMUNE® has been shown to generate an immune response faster than traditional replicating vaccines (3-4 days vs. 10-14 days).
    - It is easily administered through standard procedures such as subcutaneous (SC) or intramuscular (IM) injection.
    - It induces variola neutralizing antibodies similar to a standard Dryvax® (1st generation vaccine) vaccination.
    - It is targeted for people who have a weakened immune system.

- Imvamune® is currently an unlicensed vaccine that is still undergoing clinical trials. A phase 3 trial will reportedly begin enrolling subjects in the first half of 2013.

- Despite being unlicensed, Imvamune® is already in production and is being added to the Strategic National Stockpile (SNS). It is reported that as of May 2012, >8 million doses have already been delivered, with plans to eventually stockpile a total of 20 million doses).

- Adverse reactions (sometimes serious) to smallpox vaccination can occur.
  - In the past, for every 1 million vaccinees, 1 to 2 deaths and hundreds of complications severe enough to require hospitalization have occurred.
  - Adverse event rates tend to be much lower in revaccinees compared with primary vaccinees.
Specific adverse reactions include the following:

- Tenderness, erythema, and induration at the injection site, and other localized reactions (including allergic reactions to tape adhesives); local reactions >10 cm are referred to as "robust takes"; erythema and induration at the site can be misdiagnosed as bacterial superinfection.
- Systemic reactions, including fever of at least 100°F, malaise, myalgias, local lymphadenopathy.
- Secondary bacterial infections.
- Various dermatologic reactions, including erythema multiforme and Stevens-Johnson syndrome.
- Inadvertent autoinoculation of another body site.
- Myopericarditis: the process appears to be immunologically mediated; in Phase 3 ACAM2000® clinical trials, the rate for myocarditis and pericarditis was 5.7 per 1,000 primary vaccinees. No cases of myocarditis or pericarditis were identified in previously vaccinated subjects (although it is possible that if there had been larger numbers of previously vaccinated subjects in the trials, some cases would have been identified). The long-term outcome of myocarditis and pericarditis following ACAM2000® vaccination is currently unknown.
- Generalized vaccinia: vesicles or pustules appearing on normal skin distant from the vaccination site.
- Eczema vaccinatum: localized or systemic spread of vaccinia virus; may be severe and can be fatal.
- Vaccinia keratitis.
- Progressive vaccinia: progressive necrosis in the area of vaccination, often with metastatic lesions at other sites; can be severe and fatal.
- Postvaccinal encephalitis.
- Fetal vaccinia: occurs after primary inoculation of the mother during pregnancy; is very rare, but usually results in stillbirth or death of the infant soon after birth.

More information on adverse reactions following smallpox vaccination is available at [http://www.bt.cdc.gov/agent/smallpox/vaccination/adverse_events.asp](http://www.bt.cdc.gov/agent/smallpox/vaccination/adverse_events.asp).

Drugs that may be used in treating smallpox vaccine adverse reactions are the following:

- Vaccinia immune globulin (VIG)
  - A sterile liquid immunoglobulin G obtained from immunized donors.
  - VIG is the primary product available to treat some (but not all) serious adverse reactions to
smallpox vaccination.
- Two intravenous (IV) forms of VIG were approved by the FDA in 2005.
  - Cidofovir may be used in certain situations (under an IND protocol) to treat serious smallpox vaccine reactions.
  - Topical ophthalmic antiviral drugs may be used for ocular involvement.

- **Current use of smallpox vaccine (ACAM2000®)**
  - Smallpox vaccine is not available to the public (routine vaccination of the general population against smallpox stopped in 1972 in the U.S.).
  - ACAM2000® is provided to certain researchers and laboratory workers who may have contact with vaccinia or other orthopoxviruses, and to military personnel. Persons at continued high risk of exposure to smallpox should receive repeat ACAM2000® vaccination every three years.

- **Use of vaccine in responding to an outbreak of smallpox**
  - If an outbreak of smallpox (due to a terrorist attack) were to occur, the use of smallpox vaccine would constitute a major part of the response effort. Specific use of the vaccine in this situation is described in the following section.
  - During a smallpox emergency, all contraindications to vaccination would be reconsidered in the light of the risk of smallpox exposure. Persons would be advised by public health authorities on specific recommendations for vaccination.
  - During the smallpox eradication program, vaccination of close contacts to smallpox cases played the most important role in stopping transmission of disease. In the response to a terrorism-related outbreak, the vaccination of persons with face-to-face, household, or close-proximity contact (<2 meters = 6.5 feet) to cases (these persons are termed primary contacts) would remain a major priority.

  Vaccination of close contacts as part of the response to a smallpox outbreak is one part of a strategy called “ring vaccination” which involves:
  1. Intensive surveillance to identify smallpox cases and their contacts,
  2. Vaccinating primary contacts of the cases, and
  3. Vaccinating secondary contacts (i.e., household contacts of the primary contacts) unless they have contraindications to the vaccine.
  - According to CDC, vaccination within 3 days of exposure will prevent or significantly lessen the severity of smallpox in the vast majority of people. Vaccination 4 to 7 days after exposure likely offers some protection from disease or may modify the severity of the disease.
  - ACAM2000® provided during the response to a smallpox outbreak would be administered under an Emergency Use Authorization (EUA). Imvamune® would, according to current plans, be used under an IND protocol.
  - A system for vaccine adverse events tracking, reporting, and treatment will need to be established.

### Response to a Terrorism-Related Smallpox Outbreak
- The public health and medical response to a smallpox outbreak would likely include the following components:
  - Identification, isolation, and treatment of persons with smallpox.
  - Identification of persons who may have been exposed to the initial release of the virus.
  - Use of smallpox vaccine (ACAM2000® or Imvamune®)
    - Vaccine would be provided through the SNS, and distributed to medical facilities and to vaccination clinics.
    - Sufficient numbers of public vaccination clinics would have to be set up and staffed in order to provide vaccine to all persons for whom it is recommended. (Annex 3 of the CDC *Smallpox*

- Smallpox vaccine (ACAM2000® or Imvamune®) would be provided to:
  1. Persons who were exposed to the initial release of the virus.
  2. Close contacts of cases (primary contacts)
     - These are persons who had face-to-face, household, or close-proximity contact (< 2 meters = 6.5 feet) with a confirmed or suspected smallpox patient after the patient developed fever and until all scabs had separated (i.e., any time during the patient’s infectious period).
     - CDC states that, in general, the risk of developing smallpox for face-to-face contacts of smallpox cases outweighs their risk of developing vaccine complications, even for those with contraindications to the vaccine.
  3. Household contacts of these primary contacts (secondary contacts)
     - Household contacts of smallpox contacts who have contraindications to vaccination should consider housing themselves separately from the vaccinated (primary) contacts in order to:
       a) avoid potential exposure to smallpox should a primary contact develop the disease (thus contact would need to be avoided until the smallpox incubation period (18 days) has passed, and
       b) avoid inadvertent inoculation with vaccine virus, until the primary contact’s vaccination site has healed (i.e., until the scab at the vaccination site has separated, 14 to 21 days after vaccination).
  4. Healthcare personnel, public health personnel, first responders, law enforcement personnel, and others whose jobs put them at increased risk of exposure to smallpox.
  5. Laboratory personnel involved in the collection or processing of clinical specimens from confirmed or suspected smallpox cases.
  6. Other persons with increased likelihood of contact with infectious materials from a smallpox patient, such as laundry or medical waste handlers for a facility where smallpox patients are admitted.
  7. Other groups whose unhindered function is deemed essential for maintaining basic community needs (e.g., transportation, pharmacy, etc) and for response activities, and also those who are not otherwise involved in patient-care activities but who have a reasonable probability of contact with smallpox patients or infectious materials.
  8. Individuals present in a hospital during the time that a case was present and not yet isolated in an appropriate manner in a room with ventilation separate from other areas of the hospital should be considered for vaccination because of the potential for greater spread of smallpox in a hospital setting due to aerosolization of the virus from severely ill patients.
  9. In addition to the above, federal and state health authorities may initiate a broader vaccination campaign to enhance outbreak control if:
     a) the initial number of smallpox cases or identified locations of smallpox outbreaks is considered too large to allow contact tracing with vaccination to be effective as the only vaccination strategy for outbreak containment, and/or
     b) the risk of further smallpox releases is considered to be high.

- Note that once a smallpox attack has been discovered, there will be the need to provide vaccine to the persons listed above as quickly as possible.
- Whether or not to vaccinate persons with certain medical conditions known to be associated with a higher risk of developing severe complications to the vaccine will depend on the likelihood of exposure to variola virus. (For a description of these conditions, see the CDC fact sheet on smallpox vaccine contraindications that would apply in a pre-event vaccination program at [http://www.bt.cdc.gov/agent/smallpox/vaccination/contraindications-clinic.asp](http://www.bt.cdc.gov/agent/smallpox/vaccination/contraindications-clinic.asp). Note the statement that “during a smallpox emergency, all contraindications to vaccination...”
would be reconsidered in the light of the risk of smallpox exposure. Persons would be advised by public health authorities on recommendations for vaccination.

- Procedures will need to be developed for follow-up of vaccinated persons to confirm vaccine take.
  - A vaccine site reaction recognition card should be given to vaccine recipients at the time of vaccination.
  - If personnel resources permit, vaccine takes should be confirmed and recorded by health personnel 6-8 days following vaccination.
  - If personnel resources do not permit direct follow-up for vaccine take confirmation, recipients should be given instructions to call for evaluation if the vaccine site does not look similar to that depicted on the card at day 7.

- Mechanisms will have to be set up to handle vaccinated persons with actual or perceived adverse reactions (e.g., hotlines, guidance/consultation for medical providers, provision of drugs such as VIG in certain situations, possible establishment of special clinics, etc.).

- Primary contacts will, according to the CDC Smallpox Response Plan and Guidelines, receive smallpox vaccine and then be subject to a form of quarantine that includes fever surveillance.
  - Fever surveillance will continue until it is shown that these individuals will not develop smallpox as a result of their contact with the case – specifically, for 18 days after their last exposure to the smallpox patient, or until 14 days following successful vaccination (whichever comes first).
  - During this time, the contact is required to monitor and record his/her temperature twice daily (morning and evening) and report via telephone once daily to designated health department personnel. If resources are available, more active, closer supervision is desirable. This could include visiting asymptomatic close contacts one or more times a day.
  - Asymptomatic primary contacts may continue routine daily activities, but must remain within 20 miles of their city of residence.
  - If fever develops during this time (oral temperatures ≥101° F [38°C] on 2 successive readings), they will be isolated, medically evaluated, and treated as appropriate.

- Intensive surveillance and epidemiology activities would be undertaken. Specific activities would include identifying smallpox cases and their contacts, providing follow-up of contacts, evaluating diagnostic measures and treatment outcomes, evaluating the efficacy of the vaccines, and evaluating adverse reactions to the vaccines and the effectiveness of treatment measures.
  - Provision of information, education, and guidance to medical providers and facilities.
  - Provision of antiviral medications, VIG, and other medical supplies to medical providers as needed to treat smallpox patients and persons with certain adverse reactions to smallpox vaccine.
  - Effective communication with the public and with all those involved in the response effort. Such communication would be absolutely critical, and its importance cannot be overemphasized.

- It should be recognized that a smallpox outbreak response would require continuous, ongoing modifications based on information about the release, the course of the outbreak, public response, etc.

**Terrorism and Smallpox**

- Smallpox virus is an attractive bioweapon: 1) can be produced in large quantities; 2) stable for storage/transport; 3) known to produce a stable aerosol; 4) infection has resulted in high mortality; 5) person-to-person transmission occurs; 6) most persons have little or no immunity; 7) significant, widespread concern, and possibly panic, would result. Additionally, the impact of smallpox on the general population would be greater than during the pre-eradication era because the prevalence of
immunosuppressed individuals is higher, and because population mobility has risen dramatically, increasing the difficulty of responding to an introduction of the virus.

- The virus has been successfully weaponized for use in bombs and missiles; research was reportedly undertaken to engineer more virulent and contagious strains. The Soviet Union reportedly produced and stockpiled massive quantities of the virus for use as a biological weapon. Concern has been expressed that unfriendly nations/terrorists could potentially be in possession of the virus.

- Even if the remaining stocks of naturally-occurring smallpox virus cannot be accessed by unfriendly nations/terrorists, recent advances in synthetic biology make it at least theoretically possible to construct the virus solely from fragments produced utilizing a DNA synthesizer.

- As a bioweapon, smallpox could be transmitted by: 1) aerosol release of variola, or 2) use of an infectious person(s) to transmit infection to others.

- An aerosol release of variola virus would disseminate widely, given the considerable stability of the orthopoxviruses in aerosol form and the likelihood that the infectious dose is very small.

- Environmental survival of variola is inversely proportional to temperature and humidity. If an aerosol release of variola were to occur, 90% of virus would reportedly be inactivated or dissipated in about 24 hours.

- USAMRIID raises the possibility that weaponized smallpox strains encountered in the future may be genetically altered to render the current vaccine ineffective, a possibility experimentally validated in similar poxvirus animal models.

Other Information

- Endemic smallpox was declared eradicated in 1980 by the World Health Organization (WHO).

- Animals/insects do not carry or spread variola.

- Monkeypox
  - Caused by monkeypox virus (an Orthopoxvirus).
  - Occurs naturally in equatorial Africa, where it is described as a disease that could be clinically indistinguishable from smallpox with the exception of a generally lower case-fatality rate and notable cervical and inguinal lymphadenopathy appearing 1-2 days before the rash in 90% of cases.
  - In 2003, an outbreak of 81 primary human cases occurred in the U.S. due to exposure to exotic pets, some of which had been imported from Africa. The U.S. cases tended to be less severe, with often localized lesions only, no deaths, and no secondary transmission to other humans.

Primary Sources


5. CIDRAP. Smallpox Overview.  
   http://www.cidrap.umn.edu/cidrap/content/bt/smallpox/biofacts/index.html

6. WHO. Diagnosis of Smallpox.  
   http://www.who.int/emc/diseases/smallpox/slideset/pages/spox_001.htm

7. CDC. Smallpox Vaccination & Adverse Events Training Module.  
   http://www.bt.cdc.gov/training/smallpoxvaccine/reactions/default.htm
More Information

Smallpox – Information for Medical and Public Health Professionals (DHSS)
http://health.mo.gov/emergencies/ert/med/smallpox.php

Smallpox Vaccination – Information for Medical and Public Health Professionals (DHSS)
http://health.mo.gov/emergencies/ert/med/smallpoxvacc.php

Smallpox (CDC)

Smallpox (CIDRAP)
http://www.cidrap.umn.edu/cidrap/content/bt/smallpox/index.html

Smallpox (Comprehensive) Overview (CIDRAP)
http://www.cidrap.umn.edu/cidrap/content/bt/smallpox/biofacts/index.html

Brief Description of Selected Terms

Arthritis: Inflammation of joints due to any of a number of different causes.
Autoinoculation: Spread of infection from one part to other parts of the same body.
Bronchopneumonia: Pneumonia involving many relatively small areas of lung tissue – also called bronchial pneumonia.
Cornea: The transparent part of the coat of the eyeball that covers the iris and pupil and admits light to the interior.
Crust: An encrusting deposit that includes serum and cellular debris; a scab.
Dermal: Of or relating to skin.
Enanthem: An eruption on a mucous surface (e.g., the mouth or throat).
Eruptive: To break out (as with a skin eruption).
Erythema: Abnormal redness of the skin.
Erythematous: Relating to or marked by erythema.
Exanthem: An eruptive disease involving the skin (as measles).
Fulminant: Coming on suddenly with great severity.
Induration: A hardened mass or formation.
Inguinal: Of, relating to, or situated in the region of the groin.
In-vitro: Outside the living body and in an artificial environment.
In-vivo: In the living body.
Keratitis: Inflammation of the cornea of the eye.
Lymphadenopathy: Abnormal enlargement of the lymph nodes.
Macule: A spot or patch of skin that is altered in color but usually not elevated.
Malaise: An indefinite feeling of debility or lack of health.
Myalgias: Pain in one or more muscles.
Ocular: Of or relating to the eye.
Papule: A small solid usually conical elevation of the skin; might be described as a “bump” in the skin.
Prostration: Complete physical or mental exhaustion.
Pustule: A small circumscribed elevation of the skin containing pus; can resemble a blister but is filled with pus.
Superinfection: A second infection superimposed on an earlier one especially by a different microbial agent.
Umbilication: A depression resembling a navel.
Vesicle: A small abnormal elevation of the outer layer of skin enclosing a watery liquid; a blister.

Source: Merriam Webster Medical Dictionary

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