Y. pestis was identified in 1995 from a patient with bubonic plague in Madagascar. Although this organism was resistant to streptomycin, ampicillin, chloramphenicol, sulfonamides, and tetracycline, it retained its susceptibility to other aminoglycosides and cephalosporins. Given the subsequent identification of a similar organism in 1997 coupled with the fact that this resistance is plasmid-mediated, it seems likely that genetically modifying *Y. pestis* to a multidrug-resistant form is possible. Unlike patients with inhalational anthrax (see above), patients with pulmonary plague should be cared for under conditions of strict respiratory isolation comparable to that used for multidrug-resistant tuberculosis.

Vaccination and Prevention A formalin-fixed, whole-organism vaccine was licensed by the FDA for the prevention of plague. That vaccine is no longer being manufactured, but its potential value as a current countermeasure against bioterrorism would likely have been modest at best as it was ineffective against animal models of primary pneumonic plague. Efforts are under way to develop a second generation of vaccines that will protect against aerosol challenge. Among the candidates being tested are recombinant forms of the fraction 1 capsular (F1) antigen and the virulence component of the type III secretion apparatus (V) antigen of *Y. pestis*. It is likely that doxycycline or levofloxacin would provide coverage in a chemoprophylaxis setting. Unlike the case with anthrax, in which one has to be concerned about the persistence of ungerminated spores in the respiratory tract, the duration of prophylaxis against plague need only extend to 7 days following exposure.

SMALLPOX

See also Chap. 220e.

Variola Virus as a Bioweapon Given that most of the world's population was once vaccinated against smallpox, variola virus would not have been considered a good candidate as a bioweapon 30 years ago. However, with the cessation of immunization programs in the United States in 1972 and throughout the world in 1980 due to the successful global eradication of smallpox, close to 50% of the U.S. population is fully susceptible to smallpox today. Given its infectious nature and the 10–30% mortality rate in unimmunized individuals, the deliberate spread of this virus could have a devastating effect on our society and unleash a previously conquered deadly disease. It is estimated that an initial infection of 50–100 persons in a first generation of cases could expand by a factor of 10–20 with each succeeding generation in the absence of any effective containment measures. Although the likely implementation of an effective public health response makes this scenario unlikely, it does illustrate the potential damage and disruption that can result from a smallpox outbreak.

In 1980, the WHO recommended that all immunization programs be terminated; that representative samples of variola virus be transferred to two locations, one at the CDC in Atlanta, GA, in the United States and the other at the Institute of Virus Preparations in the Soviet Union; and that all other stocks of smallpox be destroyed. Several years later, it was recommended that these two authorized collections be destroyed. However, these latter recommendations were placed on hold in the wake of increased concerns on the use of variola virus as a biologic weapon and thus the need to maintain an active program of defensive research. Many of these concerns were based on allegations made by former Soviet officials that extensive programs had been in place in that country for the production and weaponization of large quantities of smallpox virus. The dismantling of these programs with the fall of the Soviet Union and the subsequent weakening of security measures led to fears that stocks of *Variola major* may have made their way to other countries or terrorist organizations. In addition, accounts that efforts had been taken to produce recombinant strains of *Variola* that would be more virulent and more contagious than the wild-type virus have led to an increase in the need to be vigilant for the reemergence of this often fatal infectious disease.

Microbiology and Clinical Features Smallpox is caused by one of two variants of variola virus, *V. major* and *V. minor*. Variola is a double-strand DNA virus and member of the *Orthopoxvirus* genus of the Poxviridae family. Infections with *V. minor* are generally less severe than those of *V. major*, with milder constitutional symptoms and lower mortality rates; thus *V. major* is the only one considered to be a viable bioweapon. Infection with *V. major* typically occurs following contact with an infected person. Patients are infectious from the time that a maculopapular rash appears on the skin and oropharynx through the resolution and scabbing of the pustular lesions. Infection occurs principally during close contact, through the inhalation of saliva droplets containing virus from the oropharyngeal exanthem. Aerosolized material from contaminated clothing or linen can also spread infection. Several days after exposure, a primary viremia is believed to occur that results in dissemination of virus to lymphoid tissues. A secondary viremia occurs ~4 days later that leads to localization of infection in the dermis. Approximately 12–14 days following the initial exposure, the patient develops high fever, malaise, vomiting, headache, backache, and a maculopapular rash that begins on the face and extremities and spreads to the trunk (centripetal) with lesions in the same developmental stage in any given location. This is in contrast to the rash of varicella (chickenpox) that begins on the trunk and face and spreads to the extremities (centrifugal) with lesions at all stages of development. The lesions are initially maculopapular and evolve to vesicles that eventually become pustules and then scabs. The oral mucosa also develops maculopapular lesions that evolve to ulcers. The lesions appear over a period of 1–2 days and evolve at the same rate. Although virus can be isolated from the scabs on the skin, the conventional thinking is that once the scabs have formed the patient is no longer contagious. Smallpox is associated with 10–30% mortality rates, with patients typically dying of severe systemic illness during the second week of symptoms. Historically, ~5–10% of naturally occurring smallpox cases take either of two highly virulent atypical forms, classified as *hemorrhagic* and *malignant*. These are difficult to diagnose because of their atypical presentations. The hemorrhagic form is uniformly fatal and begins with the relatively abrupt onset of a severely prostrating illness characterized by high fevers and severe headache and back and abdominal pain. This form of the illness resembles a severe systemic inflammatory syndrome, in which patients have a high viremia but die without developing the characteristic rash. Cutaneous erythema develops accompanied by petechiae and hemorrhages into the skin and mucous membranes. Death usually occurs within 5–6 days. The malignant, or "flat," form of smallpox is frequently fatal and has an onset similar to the hemorrhagic form, but with confluent skin lesions developing more slowly and never progressing to the pustular stage.

TREATMENT SMALLPOX

Given the infectious nature of smallpox and the extreme vulnerability of contemporary society, patients who are suspected cases should be handled with strict isolation procedures. Although laboratory confirmation of a suspected case by culture, polymerase chain reaction (PCR), and electron microscopy is essential, it is equally important that appropriate precautions be used when obtaining samples for culture and laboratory testing. All health care and laboratory workers caring for patients should have been recently immunized with vaccinia, and all samples should be transported in doubly sealed containers. Patients should be cared for in negative-pressure rooms with strict isolation precautions.

There is no licensed specific therapy for smallpox, and historic treatments have focused solely on supportive care. Although several antiviral agents, including cidofovir, that are licensed for other diseases have in vitro activity against *V. major*, they have never been tested in the setting of human disease. For this reason, it is difficult to predict whether or not they would be effective in cases of smallpox and, if effective, whether or not they would be of value in patients with advanced disease. Agents currently being studied as possible antiviral compounds against *V. major* include a viral egress inhibitor (tecovirimat, ST-246, or Arestvyr) and a lipid-conjugated form of cidofovir (brincidofovir, CMX001).