Nebraska Isolation and Quarantine Manual
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Variola Virus (Smallpox)

HISTORY

Smallpox has been one of humankind’s greatest scourges since before recorded history. Few diseases, including plague, yellow fever, or cholera have impacted human populations and history as dramatically. The origin of smallpox is obscure, but it is believed to have appeared at the time of the first agricultural settlements in northeastern Africa around 10,000 BCE. The original animal reservoir was probably a rodent that has since become extinct. In small populations, the disease would burn itself out once all members of the village or community had been infected, and not until population densities of about 200,000 developed was it able to sustain itself in humans. The earliest evidence of skin lesions resembling those of smallpox is found on the faces of mummies from the time of the 18th and 20th Egyptian dynasties (1570 to 1085 BCE) and on the well-preserved mummy of Ramses V, who died as a young man in 1157 BCE. The first recorded smallpox epidemic occurred in 1350 BCE during the Egyptian-Hittite wars. The illness was passed to the Hittite population by Egyptians, infecting the Hittite king, Suppiluliumas I, and his heir, Arnuwandas, and precipitating a sharp decline in their civilization.

Smallpox greatly affected the development of Western civilization. Smallpox and measles were introduced into the New World by the Span-
ish, and over the course of about 100 years between 1518 and 1620, the population of Mexico declined from 25 million to 1.6 million, in part due to such infection introductions. In Europe, by the end of the 18th century, an estimated 400,000 persons died annually from smallpox, and survivors accounted for one-third of all cases of blindness. During the 18th century, 5 reigning European monarchs died of smallpox, and the Austrian Hapsburg line of succession shifted 4 times in 4 generations.

**MICROBIOLOGY**

Smallpox is caused by variola (from Latin the diminutive varius, meaning spotted) virus, a DNA virus member of the genus Orthopoxvirus in the Poxviridae family. The orthopoxviruses are among the largest and most complex of all viruses, which serologically cross-react, and appear to offer cross-protection against infection. Smallpox is caused by two closely related but genetically distinct viruses, Variola major (typical smallpox) and Variola minor (alastrim). Clinically they are similar, but Variola minor cases are associated with fewer symptoms, less extensive rash, less scarring, and much lower mortality. Three other members of the Orthopoxvirus family also cause disease in humans: vaccinia (the basis of current smallpox vaccines), monkeypox (see below), and cowpox.

**PATHOGENESIS OF DISEASE**

The infectious dose for variola is unknown but may be as low as only a few virions. Typical infection begins after deposition of the virus on the oropharyngeal or respiratory mucosa. The virus is usually transmitted by contact or in droplets expressed from nasal and oropharyngeal secretions. While cough is not a typical symptom of smallpox, when cough is present the virus can be expelled as a fine-particle aerosol. After replication in local tissues, the virus then migrates to, and multiplies in, regional lymph nodes.

Asymptomatic viremia develops on about the 3rd or 4th day, with virus migrating from regional nodes to the organs of the reticuloendothelial system including liver, spleen, bone marrow, and distant lymph nodes, where replication continues. Secondary viremia begins on about the 8th day and is followed by clinical manifestations. The virus, con-
tained in leukocytes, then localizes in small blood vessels of the dermis and below the oral and pharyngeal mucosa, where it subsequently infects adjacent cells, leading to the typical manifestations of exanthem and enanthem.

**CLINICAL MANIFESTATIONS**

The incubation period is characteristically 12 days, with a range of 7–17. The first clinical sign of infection is a prodromal illness, corresponding with the secondary viremia phase, characterized by the abrupt onset of malaise, fever that may exceed 40°C, constitutional symptoms, vomiting, and delirium. Around the 3rd or 4th day buccal and pharyngeal lesions begin to appear. Rash begins on the face and spreads to the forearms and hands, and then to the lower limbs and trunk. Lesions, which are always more prominent on the face, begin as macules and quickly evolve to papules and then to vesicles over a few days. Pustules appear about the 8th day of illness. The round and tense pustules are deeply embedded in the dermis and thus are firm to the touch. Pustules eventually dry and form scabs, which leave scars after flaking off.

Mortality from *Variola major* was reported to be from 20% in some communities to as high as > 50% in totally naive communities such as Native Americans. The most commonly quoted overall mortality rate is 30%. However, since the virus was eliminated 4 decades ago before the onset of the HIV pandemic and medical advances allowing longer survival of immunocompromised individuals of all types, and most individuals do not receive the vaccine, the untreated mortality rate today would be expected to be much higher. Death, if it occurred, usually happened in the second week of illness and was attributed to immune complex mediated shock. More severe clinical presentations believed to be related to impaired cellular immune response yielded hemorrhagic or “flat type” smallpox cases, who never developed the typical smallpox lesions; these infections were nearly universally fatal.

**DIFFERENTIAL DIAGNOSIS**

Clinical diagnosis remains the most important step for suspecting and ultimately confirming a reemergence of smallpox. Febrile exanthems
are common, and many eruptive skin lesions were historically misinterpreted as smallpox. Severe varicella (chicken pox) and monkeypox are probably the diseases most likely to be misidentified, as well as erythema multiforme with bullae, disseminated herpes zoster, impetigo, and severe contact dermatitis. On rare occasions, patients who are immunized with the smallpox vaccine (vaccinia) can develop disseminated vaccinia infection. A careful history and physical will be important in establishing the correct diagnosis. Typical smallpox always begins with a febrile prodrome prior to the exanthem. In addition, lesions are centrifugal in distribution (concentrated in the face and distal extremities, while more sparing on the trunk), and they progress in slow synchrony. With varicella, lesions are more centrally distributed, evolve rapidly and at different stages, and generally appear concurrently with onset of fever. Varicella lesions are delicate and superficial (dewdrops on a rose petal), and are almost never found on the palms or soles, as opposed to variola lesions, which are firm and deep. Monkeypox lesions are quite similar to smallpox, but monkeypox infections are often distinguishable by epidemiology and the frequent presence of cervical and inguinal lymphadenopathy.

**DIAGNOSIS**

The identification of even a single suspected case of smallpox should be treated as an international health emergency and brought immediately to the attention of national officials through local and state health departments.

The Centers for Disease Control and Prevention (CDC) has developed a diagnostic algorithm for clinicians (see https://www.cdc.gov/smallpox/clinicians/algorithm-protocol.html). Specimens for testing of potential smallpox patients should only be collected by an individual who has been recently vaccinated (or is vaccinated that day) and is wearing appropriate personal protective equipment (PPE). Vesicular or pustular fluid is obtained by opening the lesions with the blunt end of a scalpel. The fluid is then absorbed onto a cotton swab. Alternatively, scabs can be picked off with a forceps. Specimens should be bagged or stoppered and then placed in a sealed, puncture-proof container for transport. The CDC maintains a website where specifics and assistance can be provided (http://emergency.cdc.gov/agent/smallpox/response-plan/files/guide-d.pdf) and their hotline number is 800-232-4636 (800-CDCINFO).
Orthopox infection can be confirmed rapidly by electron microscopic (EM) examination of vesicular or pustular fluid or scabs. Although all orthopoxviruses exhibit identically appearing brick-shaped virions, the history and clinical picture should help differentiate the illness from cowpox, monkeypox, or vaccinia infections. Definitive laboratory identification and characterization of the virus involves growth of the virus in cell culture or on chorioallantoic egg membrane and characterization of strains by use of various biologic assays, including polymerase chain reaction, and restriction fragment length polymorphism.

TREATMENT

While some weak evidence suggested mortality reduction with use of vaccinia immune globulin (VIG) or convalescent serum, no universally accepted or licensed therapeutics existed for smallpox prior to eradication. Fortunately, renewed emphasis on smallpox countermeasures in US civilian and military biodefense research in the early 2000s resulted in a number of new candidates, including tecovirimat (TPOXX®, formerly ST-246), a new orthopoxvirus-specific antiviral drug. In July 2018, oral tecovirimat was approved in the United States for treatment of smallpox in adults and pediatric patients weighing ≥ 13 kg. The recommended dosage of tecovirimat for those weighing ≥ 40 kg is 600 mg BID. For pediatric patients weighing between 25 and 40 kg, the dose is 400 mg BID, and for those between 13 and 25 kg, 200 mg BID. The duration of treatment is 14 days. An intravenous formulation of the product is undergoing phase I development. This agent is only available through the US government’s Strategic National Stockpile (SNS). Cidofovir, an FDA-licensed intravenous antiviral, has also been shown to have efficacy against orthopoxviruses in animal models of infection. Brincidofovir is an analog of cidofovir formulated for oral administration that may have fewer adverse effects compared to cidofovir. It is undergoing testing as an additional therapeutic agent.

VACCINES

All smallpox vaccines currently in use are derived from vaccinia virus, an orthopoxvirus whose origins and natural host are unknown. The most commonly used vaccine strain in the United States was the New York
City Board of Health strain from which Dryvax and then ACAM2000 were derived. Dryvax, the previous stockpiled standard US vaccinia vaccine, has been phased out, and the vaccine that is currently used is ACAM2000, derived from Dryvax but grown in cell culture. The SNS currently stockpiles sufficient ACAM 2000 to vaccinate the entire US population if needed. Other countries used different strains of vaccinia virus, including the Lister (or Elestree) strain (UK), EM-63 (Russia), Temple of Heaven (China), Padwadanger (India), and LC16m8 (Japan). While all appear to have relatively similar efficacy, the frequency of adverse events may vary by strain.

For individuals with a recent history of smallpox exposure, postexposure vaccination as soon as feasible and within up to 96 hours may prevent, or at least ameliorate, disease. While not approved for post exposure prophylaxis, tecovirimat offers an alternative to this, with minimal side effects. Use of tecovirimat as PEP would be a topic for discussion in the event of an outbreak of smallpox.

Vaccine is administered via scarification and results in development of an eschar (the only marker for successful vaccination), which leaves a visible scar in most individuals and therefore permanent evidence of vaccination. Vaccination is often associated with fever, local inflammation, and lymphadenopathy. Historically, the vaccine caused more severe side effects in approximately 75 per one million recipients. The most commonly reported serious adverse events are progressive vaccinia (vaccinia necrosum), eczema vaccinatum, and vaccinial encephalitis, and death occurs in roughly one per million primary vaccinees. Adverse events are most commonly seen after initial vaccination, and frequency diminishes dramatically with subsequent administrations. Contraindications to receipt of ACAM 2000 in the nonemergency setting include patients with immunodeficiencies, individuals with eczema or other exfoliative skin condition, pregnant women, anaphylaxis to polymyxin and neomycin (trace amounts of these agents are present in the vaccine), or close contacts with immunocompromised patients. In situations with bona fide exposures to smallpox, vaccination with a live vaccinia preparation has historically been considered reasonable despite typical contraindications, although modified vaccinia Ankara (MVA) might now be considered an alternative.
In 2003 the US Department of Health and Human Services implemented a smallpox vaccination program with Dryvax for potential first responders. In 38,000 administrations, there were 822 reported adverse events, 100 of which were considered serious. Adverse events included myocarditis and pericarditis (21 cases) and unexpected ischemic cardiac events (10 cases). On the basis of this, additional contraindications to the vaccine were added, of either a history of cardiac disease or the presence of 3 major risk factors for atherosclerotic heart disease (hypertension, diabetes, hypercholesterolemia, smoking, or a history of heart disease in a first-degree relative before the age of 50).

MVA, manufactured under the name Imvamune, is a third-generation nonreplicating vaccine that has been used in a number of human trials and is currently approved for use in Europe and Canada. It has an improved safety profile in humans when compared to replication competent smallpox vaccines, but its efficacy is not as well characterized. It is intended for use in individuals for whom the use of ACAM 2000 is contraindicated. The vaccine is administered as a 0.5 ml subcutaneous injection at days 0 and 28 for primary vaccines. There is no eschar associated with this product. Imvamune is an investigational product that is also stored in the SNS.

**ISOLATION**

Suspected smallpox patients should be placed under contact and airborne isolation. Patients are most infectious from the onset of the enanthem through the first 7–10 days of rash. The infectiousness of an individual patient is primarily related to the extent and severity of the enanthem in the mouth and throat. As scabs form, even though the scabs contain large amounts of viable virus, the virions appear to be tightly bound to the fibrin matrix and thus pose much less risk of transmission. Despite that, patients should be considered potentially contagious until all eschars have fallen off.

Transmission of smallpox generally occurred with prolonged and extensive contact, and secondary cases were most commonly seen in those who lived with or cared for ill patients, usually in the household or hospital. Although smallpox is much less transmissible than measles, primary varicella, or influenza, secondary attack rates among unvacci-
nated contacts range from 37% to 88%. In certain cases, patients who are coughing can transmit large quantities of virus by aerosol. In Meschede, Germany, 17 persons on 3 floors of a hospital contracted smallpox from a patient admitted for a febrile illness presumed initially to be typhoid fever; this outbreak was ascribed to the patient’s cough and the low relative humidity and air currents in the hospital.

At room temperature and relatively low humidity the virus survives in crusts from infected patients for as long as 16 weeks. Thus both fomite transmission from such items as bedsheets and blankets has been documented. A number of laundry workers who handled linens and blankets used by patients have developed disease. Disinfectants that are used for standard hospital infection control, such as hypochlorite and quaternary ammonium compounds, are effective for cleaning surfaces possibly contaminated with the virus.

Ideally only vaccinated persons should care for the patient. If there is an inadequate number of vaccinated individuals, vaccination of additional personnel should be done, immediately after which they are able to care for the patient. The long incubation period of variola infection allows the vaccine to modify the course of illness after exposure.

QUARANTINE

Smallpox was one of the standard internationally quarantinable diseases until its elimination, and it specifically remains on the US list of federally quarantinable diseases. Therefore, patients with suspected contact with smallpox patients could be detained by health authorities for monitoring. With options for vaccination postexposure, it is reasonable that any quarantine period might be limited on vaccination with appropriate postvaccination follow-up to ensure successful vaccination and interruption of disease transmission. Additionally, options such as home quarantine would be reasonable to consider, with additional vaccination of household members.

Monkeypox

HISTORY

The term “monkeypox” is a misnomer, based on the original isolation of the virus in 1958 from a colony of ill monkeys kept for research. While it
has only been isolated once from a wild animal (a squirrel in the Democratic Republic of the Congo [DRC]), one or more species of rodents that inhabit the secondary forests of Central Africa are presumed to serve as the natural reservoirs. Monkeypox differs from variola in its ability to infect and cause illness outside of its reservoir species, and both non-human primates and humans develop clinical illness, which may prove fatal. Human monkeypox was not recognized as a distinct infection in humans until 1970 during efforts to eradicate smallpox, when the virus was isolated from a patient with suspected smallpox infection.

**MICROBIOLOGY**

Monkeypox virus is an orthopoxvirus in the same genus as variola and vaccinia. As with other orthopoxviruses, there appears to be significant cross-protection with vaccinia and variola infection. Two distinct geographic strains of the monkeypox virus exist. The Central African strain is more virulent, with mortality rates as high as 10%. The Western African strain lacks several genes compared to the Central African strain and causes less severe disease.

**EPIDEMIOLOGY**

Monkeypox has probably affected humans in endemic areas for millennia. Transmission from rodents to humans occurs from the handling of rodents used for bushmeat, as well as bites, scratches, and exposure to infected body fluids. Human-to-human transmission appears to be less efficient than for smallpox; however, it was seen to occur in up to 11.7% of household contacts of patients who had not received the smallpox vaccination. Household contacts and those caring for a monkeypox patient are at increased risk for acquiring infection.

Recently there have been outbreaks reported in several Central African countries. Waning immunity as well as increased dependence on hunting for food in areas devastated by civil war have been considered the most likely explanations for this increase. In 2003 an outbreak of human monkeypox (West African strain) occurred in the United States as the result of exposure to infected prairie dogs that had been housed close to rodents imported from Africa. There were 71 identified cases and no fatalities.
PATHOGENESIS

Disease pathogenesis is similar to that described for variola (above). After exposure by one of the routes noted above, the incubation period ranges from 9 to 13 days, shorter with either a larger inoculum or with percutaneous, as opposed to mucous membrane, exposure and accompanied by more severe disease manifestations.

CLINICAL MANIFESTATIONS

Based largely on sero-epidemiological studies in Africa, the majority of monkeypox infections are associated with mild nonspecific illness or are asymptomatic. Many of the clinical characteristics of human monkeypox infection mirror those of smallpox. Rash is preceded by a few days by fever, headache, myalgias, and lymphadenopathy affecting submental (causing jaw pain), cervical, and inguinal nodes. Enlarged lymph nodes are firm, tender, and sometimes painful. Rash often first appears on the face and quickly develops in a centrifugal distribution. Lesions can also involve mucous membranes, and oral lesions can cause difficulty with eating and drinking. The rash usually begins as macules and papules, which progress over approximately 2 weeks to vesicles and pustules. Similar to smallpox, all lesions evolve in the same stage of development, a critical differentiation from varicella (chicken pox). Pustules crust over after 1 to 2 weeks and then desquamate. The duration of illness is approximately 4–5 weeks from onset of the prodrome. Mortality rates from the Central African strain may be as high as 10%.

DIAGNOSIS

The diagnostic algorithm mentioned above for smallpox is useful in evaluating a possible case of monkeypox. History and clinical features aid in establishing the diagnosis, but definitive confirmation is established by virus isolation, real-time PCR, or immunofluorescent assay, all of which are done in a reference laboratory. Recognition of characteristic brick-shaped virions on electron microscopy (EM) distinguishes monkeypox from varicella, but the appearance on EM is identical to variola.
DIFFERENTIAL DIAGNOSIS
Varicella is the major disease in the differential, and distinguishing characteristics of monkeypox include lymphadenopathy and cutaneous lesions being in similar stages of development/healing. Additional vesiculopustular rash illnesses included in the differential are other herpetic infections, drug rash, syphilis, yaws, and scabies. Tanapox is another African poxvirus that causes a viral prodrome and skin lesions. Orf and bovine stomatitis can produce localized skin lesions but have a different appearance under EM.

TREATMENT
Tecovirimat, a recently licensed drug for treatment of smallpox, has activity against monkeypox. It has been shown to protect nonhuman primates from a lethal monkeypox challenge. See above discussion of use for smallpox. Brincidofovir also has the potential for activity against human monkeypox.

VACCINATION ISSUES
Vaccination against smallpox provides protection against other orthopoxvirus infections, including monkeypox. Whereas the degree of protection is less than complete, disease severity is significantly less in vaccinated individuals. In the US outbreak, 6 of 29 evaluated cases of symptomatic disease (24%) had received prior childhood smallpox vaccination. There was a trend toward milder disease in these individuals. Studies conducted in the DRC from 1981 to 1986 in the days following smallpox eradication showed that the attack rate of household members was significantly lower among those who had prior smallpox vaccination than among those without vaccination. Prior vaccination conferred 85% protection against monkeypox.

ISOLATION
Transmission of monkeypox is likely a rare event in the health care setting. The use of contact and airborne isolation precautions are recommended for any generalized vesicular rash of unknown etiology in
which monkeypox and smallpox are in the differential diagnosis. Similar to variola, the virus is likely to survive for longer periods in low-humidity environments. Routine hospital cleaning agents are sufficient to kill monkeypox virus.

**QUARANTINE**

Monkeypox is not on the list of federally quarantinable diseases nor in the international health regulations. However, given its similarity to smallpox in clinical presentation, for individuals who have been exposed to someone with a smallpox-like illness, active monitoring or some restriction of movement might be considered until the symptomatic case is determined to be monkeypox rather than smallpox. Vaccination may be considered a potential option for exposed individuals, depending on the extent of presumed exposure.