

## Monkeypox (Summary)

Human monkeypox disease has most commonly occurred following the consumption of an infected food source (such as primates or rodents in Africa) or from the direct contact with body fluids from an infected individual or animal. Our understanding of the histopathology of monkeypox virus infections in humans is limited but it is believed to be similar to that observed with smallpox. The incubation period of the disease following exposure to the onset of fever is about 12 days. The disease course progresses quickly once the patient becomes viraemic. Clinical signs include:

- Fever of  $>99.3^{\circ}\text{F}/37.4^{\circ}\text{C}$
- Productive cough, sore throat, shortness of breath, headache, backache, malaise, chills and/or sweats, vomiting
- Generalized lymphadenopathy (not observed with smallpox) is more frequently observed in primary cases
- Centralized or localized rash which evolves shortly after the onset of fever (macular, papular, vesicular then pustular)
- Hyper-pigmentation or scarring are uncommon following the desquamation of resolved lesions, and corneal lesions leading to blindness occur rarely
- Enanthem in the oral cavity may occur more often in primary than secondary cases
- Like smallpox infection, patients should be considered infectious until all scabs separate

### Diagnosis & Treatment

**Diagnostic Samples:** Pharyngeal swab, scab material, serum

**Differential Diagnosis:** varicella, molluscum contagiosum, measles

#### **Isolation/Decon Precautions**

- Victim (overt attack): Undress, soap, and shower.
- Responder: Surveillance and containment (maintain minimum 17d or until all scabs separate)
- Environment: 0.5% bleach or hot soapy water
- Fomites: Exercise respiratory and skin contact precautions when handling infected bedding or clothing prior to laundering.
- Scabs separated from patients may remain infectious for several days or longer under ideal conditions.

#### **Therapy**

- Smallpox vaccine Give immediately, unless contraindicated, if previous vaccination was  $> 3\text{y}$  before. Even in previously unvaccinated individuals, effective if given within 3 to 4 days following exposure.

- Cidofovir (pediatric dosage is not yet established) possibly effective, at least prophylactically, based on in vitro and animal data. Cidofovir therapy is not FDA licensed for the treatment of *Orthopoxvirus* infections.
- Supportive therapy plus antibiotics to preclude secondary infection may be indicated.
- Steroid therapy may exacerbate the disease and is contraindicated for *Orthopoxvirus* infections.

### **Prophylaxis**

- Vaccination with the smallpox vaccine. A single dose (0.5ml) by scarification using a bifurcated needle in the upper left deltoid following the WHO guidance for smallpox vaccine administration is recommended: (<http://www.who.int/emc/diseases/smallpox/factsheet.html>).

## Monkeypox (Extensive Information)

Monkeypox virus, a classic zoonotic agent, was first identified during an outbreak among jungle inhabitants from Zaire (formerly the Democratic Republic of the Congo) in 1970 as a new “variola-like” virus that could cause disease in humans. In fact, monkeypox occurs as an indigenous rodent-borne disease among wild non-human primates throughout the rain forests of central and western Africa and its description as a vesicular disease in monkeys has been recited in the classic literature since as early as 1861. It is a member of the same family (*Poxviridae*), subfamily (*Chordopoxvirinae*) and genus (*Orthopoxvirus*) as variola virus, the causative agent of smallpox. The evolution and distribution of the pustular rash (exanthema) in human cases of monkeypox disease observed during outbreaks in Africa have been reported to be clinically similar in appearance to ordinary-discreet or modified-type (varioloid) smallpox. The case fatality rate for human monkeypox infections during outbreaks in Africa in the late 90’s approached 2% and was highest in young children aged less than 8 years. This revised case fatality rate is much lower than previously reported (10%). A milder clinical disease resulting in no fatalities was observed during the human outbreak in the United States in 2003. Conventional wisdom suggests that vaccination with the smallpox vaccine (vaccinia) is protective against or may attenuate monkeypox infection.

- History of Monkeypox
- Current Threat of Monkeypox Biological Weapons
- Epidemiology and Epizootology
- Classification and Etiology
- Organ and System Pathogenesis
- Clinical Manifestations and Diagnosis
- Subjective and Objective Symptoms
- Differential Diagnosis
- Diagnostic Samples and Related Biosafety Issues
- Protection, Isolation and Notification
- Vaccination and Post-Exposure Prophylaxis and Treatment
- Sources of Additional Information
- References

## History of Monkeypox

The number of persons that were infected with monkeypox while smallpox was still endemic in the western and central parts of Africa remains unknown. It is likely that outbreaks of human monkeypox in these regions were mistakenly identified as smallpox, at least until endemic smallpox was eliminated from Zaire in 1968. When the first cases of human monkeypox were observed in 1970, it was initially thought by WHO investigators that a re-introduction of variola virus had occurred from an imported case of smallpox. When the importation of smallpox into Zaire was initially ruled out and the likelihood of a simian reservoir considered, the implications were at first quite shocking. Had an animal reservoir for variola virus existed, then the global campaign to eradicate smallpox would have been impossible. Only through the careful laboratory analysis of serological specimens collected from persons suffering from this “smallpox-like” illness did investigators discover that this outbreak was caused by a similar *Orthopoxvirus* – monkeypox. Several outbreaks of monkeypox, all with low mortality, have occurred in Africa over the course of two decades, before the recent outbreak in the United States.

### **The Death of Smallpox: Our Introduction to Monkeypox**

After the eradication of smallpox and the cessation of routine smallpox vaccination, monkeypox has become the most significant *Orthopoxvirus* infection for humans. Monkeypox virus can cause a mild to severe disease in unvaccinated persons that resembles the milder forms of smallpox often caused by infection with variola minor virus. There have been no reported instances of human monkeypox infection that resemble those caused by variola major virus, which can result in the development of the ordinary confluent, flat-type, or hemorrhagic forms of smallpox that were responsible for case fatality rates of 30%, 95%, and 99% respectively. Before 2003, monkeypox infections had not occurred outside of the suspected rodent reservoirs’ natural habitat within the African continent.

With the exception of the recent importation of this disease, monkeypox generally has not been considered to be a public health threat in the U.S. Current epidemiological evidence indicates that the transmission potential of monkeypox throughout an un-immunized population is quite low and that a sustained chain of transmission throughout a human community does not occur. *Orthopoxviruses* like monkeypox and variola virus are host specific: they may cause a transient infection in one host system but their full pathological effects have been observed only in their natural host species. There is no evidence to support assertions that monkeypox virus may evolve to fill the ecological niche left by variola virus.

The availability of an efficacious vaccine, better nutrition, and access to good healthcare have been cited as reasons for the successful identification, interdiction, limited morbidity and effective treatment of human monkeypox cases in the U.S. Notably, the incidence of a much milder disease with no deaths reported during the U.S. outbreak, as opposed to those reported from Africa, suggests that the national health care network is better prepared to respond to future natural outbreaks of monkeypox.



## Current Threat of Monkeypox Biological Weapons

The actual threat posed by an illicit release of monkeypox virus upon a human population is debatable. To a terrorist group seeking a biological weapons capability, monkeypox virus might present an attractive surrogate for variola virus. On the other hand, our recent success in containing the monkeypox outbreak in the US might serve as a deterrent to its use.

It is known that humans can become infected with monkeypox following intimate contact with a rodent or primate host suffering from the disease. The primary route of exposure resulting in disease in unvaccinated humans has been gastrointestinal; cutaneous exposure is strongly suspected in cases of auto-inoculation\*. Gastrointestinal exposure to monkeypox virus is known to cause a more severe disease in humans than other routes of exposure, such as the bite from a diseased animal.

Droplet spread by persons presenting with respiratory complications during outbreaks in Africa has been reported rarely, suggesting that it might be an inefficient mode of transmission. Moreover, the respiratory transmission of monkeypox infections reported from African outbreaks is thought to have occurred during [very] close contact; furthermore, this method of transmission could likely not be reliably sustained beyond secondary cases. This suggests that monkeypox virus is a much less contagious disease for humans than variola virus. If monkeypox virus were to be disseminated as an illicit biological aerosol it might not remain viable in the open environment long enough to enter a susceptible host and initiate an infection. Accordingly, the aerogenic inoculum required to cause fulminate disease in humans ( $ID_{50}$ ) is not known.

A terrorist group might very well desire to acquire a pathogen that is known to cause an incapacitating or fatal disease in people, is contagious, and is not treatable. The potential problems that could be encountered by a terrorist group laboring to produce an effective monkeypox agent are numerous and any number of them may not be solvable. Unless monkeypox is made more virulent or pathogenic for humans and more biologically stable or infectious via the respiratory route, its potential utility as a possible biological weapon is limited.

\* Auto-inoculation can occur from direct contact with the pustule fluid from weeping pox lesions on the skin of an infected or vaccinated person. Rubbing ones' eyes, wiping of the mouth, eating, or contact through a cut or abrasion on the skin without washing of the hands are common causes of auto-inoculation exposure. This has been reported with vaccinia in persons after vaccination with the smallpox vaccine.

## Epidemiology and Epizootology

Humans are not a natural reservoir host for monkeypox virus. In non-human primates, monkeypox virus produces a severe and oftentimes fatal disease very similar to human smallpox – hence its surname. Monkeypox virus has been isolated from several species of African rodents but no single species has been implicated as the definitive host reservoir.

Upon initial examination, clinical presentation of fulminate monkeypox infection may closely resemble variola minor virus infection. Fortunately, there are several distinguishable epidemiological features present with human monkeypox infection that have not been observed with smallpox.

- Monkeypox virus infection can occur through ingestion or cutaneous exposure and respiratory exposure is suspected to have occurred by droplet aerosol.
  - Smallpox infection has primarily occurred from droplet aerosol (e.g. coughing) and/or through cutaneous exposure (i.e. variolation). There have been no reported incidences of smallpox via GI tract exposure.
- Monkeypox is not known to result from mechanical transmission e.g. insects or from environmental fomites.
  - Smallpox transmission commonly occurred from exposure to fomites (infected bed linens or clothing, blankets, etc...); transmission from an insect vector is suspected, but unconfirmed.
- Monkeypox transmission rarely occurs beyond secondary cases.
  - Smallpox transmission was sustained in a human population and was responsible for numerous devastating epidemics since antiquity.
- Children are reported to be more susceptible to monkeypox infection than adults.
  - Smallpox infection had no predilection for any particular age group. however pregnant women were more prone to develop the hemorrhagic form of the disease.

Physical protection combined with vaccination can prevent infection against monkeypox virus. Overt disease may be prevented if vaccine is administered 2-4 days following a known exposure to a confirmed case of monkeypox; after that time but before the onset of rash, vaccination may help reduce the severity of disease and could prevent mortality. Human monkeypox cases should be considered infectious until the scabs resolve. Domestic pets, and most importantly pet rodents, may play a role in transmitting monkeypox within a household and should be quarantined until the last case is fully recovered.

Infections are not definitively known to have occurred from exposure to or handling of the corpses of monkeypox or smallpox victims as they have from handling linens and other fomites; however, appropriate precautions should be observed when working with corpses.

## Classification and Etiology

Monkeypox virions are characteristically similar in appearance to variola virus when examined by electron microscopy. The morphological structure of monkeypox virus does bear some differences to the variola, vaccinia, and cowpox viruses though they are antigenically similar. Monkeypox virions are brick-shaped with a distinct “dumb-bell” shaped lateral core measuring approximately 250nm by 200nm. The monkeypox virus genome is 191kbp and contains a covalently closed, single linear double-stranded DNA molecule with inverted terminal repeats and a hair-pin loop at each end. The structure of the viral membrane consists of well-defined surface tubules giving it a characteristic ribbed appearance. Like all other Orthopoxviruses, monkeypox replicates within the cytoplasm where the outer membrane of the developing mature virus particle becomes wrapped by the modified Golgi network and then transported to the periphery of the cell wall. Monkeypox virus and all other *Orthopoxviruses* produce haemagglutinin. Intracytoplasmic inclusion bodies of the A- and B-type can be found upon examination of biopsy material using electron microscopic techniques; variola virus does not produce the A-type. Enveloped and non-enveloped virions are infectious. Monkeypox virus forms small whitish plaques very similar to those produced by variola virus on the chorioallantoic membrane (CAM) of embryonated chicken eggs with a ceiling growth temperature of 39<sup>0</sup>C; however at 35<sup>0</sup>C, monkeypox virus produces small red hemorrhagic plaques on the CAM. This is a useful laboratory test to distinguish it from variola virus which produces small glossy white, non-ulcerated plaques on the CAM at incubation temperatures between 35<sup>0</sup>C - 38.5<sup>0</sup>C.

## Organ and System Pathogenesis

In the US, most confirmed human monkeypox infections have manifested following the direct contact with an infected pet rodent; exclusive human-to-human transmission has been strongly suspected but not confirmed. The potential for inter-human spread of the disease should not be dismissed. Virus transmission via respiratory droplet spread was reported during outbreaks of the disease in Africa, albeit very rarely. Monkeypox lesions are generally described as necrotizing, a feature not associated with smallpox.

Monkeypox infection enters the body either by the cutaneous, airways, conjunctivae, or GI route of exposure. The sequence of virus replication is similar to that of other *Orthopoxviruses*: the virus replicates in the lymphatic system, leading to passage in the blood stream, and multiplication within the epithelial cells of the skin. In experimentally infected non-human primates, concurrent infection can involve the spleen, liver, and in some rare cases the bone marrow. The degree of virus distribution within other organs during human cases of monkeypox infection is not clearly understood but it is suspected to be an uncommon to rare occurrence.

The molecular pathogenesis and pathology of experimental *Orthopoxvirus* infections in a susceptible animal model have been well described in the scientific literature. There are no indications that monkeypox virus becomes more virulent, pathogenic, or more transmissible by passage through a human host. Yet, a better understanding of the clinico-epidemiological features of human *Orthopoxvirus* infections would certainly benefit our ability to develop efficacious vaccines, therapies, and possibly a cure for human-transmissible poxvirus infections.

## Clinical Manifestations and Diagnosis

There are three known types of human monkeypox infection that have been observed, based upon the distribution of skin lesions:

1. **Discrete:** The majority of primary and secondary cases examined in Africa (>60%) and the US (>90%) involved a sparse, disseminated macular eruption that may or may not go clinically unnoticed. Lesions may be similar in appearance to varioloid.
2. **Semi-confluent:** Observed in both primary and secondary cases (~32%). Distribution of the rash is centralized and described as moderate; may look clinically similar to ordinary-discrete smallpox.
3. **Confluent:** Uncommon for primary cases (<13%) and very rare for secondary cases (<2%). Appearance and distribution of the rash is more akin to ordinary semi-confluent smallpox.

There has been no significant difference observed in the severity or duration of illness, the frequency of complication or sequale, or the crude case fatality rates based upon the intensity and distribution of the rash.

### Duration

The clinical course of human monkeypox infection after exposure is similar to human smallpox with few, but key exceptions:

1. The incubation period: Virus replication is similar to that of smallpox. Patient is asymptomatic until the onset of fever, which may present 7 to 17 days after exposure.
2. Prodromal period: Begins with the rapid onset of fever (viraemia), which may last 1-3 days. Patients are not considered contagious during this period. In most cases (>90%) pronounced lymphadenopathy presents during the prodrome.
3. Manifestation period: The cutaneous eruption of the pustular rash begins after the end of the prodrome and evolves in the same stage as smallpox beginning with a rash, then macules, papules, vesicles, and finally pustules, which crust over the course of 14 to 21 days. The distribution of lesions is described as peripheral. Lesions on the face and extremities are not described as confluent comparable to smallpox. During development, the pustules may vary in size; therefore, could be mistakenly diagnosed as chickenpox lesions. Enanthem in the oral cavity with acute tonsillitis has been observed more frequently with primary cases than with secondary cases. Encephalitis is an extremely rare occurrence but it is not known to cause permanent neurological sequale; a full recovery for these patients is expected.
4. Outcome: Complete recovery is expected for the majority of cases affected, although death can occur in the most severe cases. Separating scabs may leave depigmented spots that resolve in a few months. Pitted scarring, resulting from the destruction of the sebaceous glands, may be present in half of the cases infected but these pock-marks may resolve within 5 years.

## Subjective Symptoms

The symptoms of monkeypox infection and their duration are described below:

1. Fever: Rapid onset of fever  $>99.3^{\circ}\text{F}/37.4^{\circ}\text{C}$  that subsides after 1-3 days. Soaking sweats are common.
2. Pain: Headache, severe backaches, sore throat.
3. Fatigue/malaise: common throughout the manifestation period. Symptoms begin to subside after 2 weeks.
4. Respiratory: productive cough, bronchopneumonia, shortness of breath.
5. Nausea: uncommon, but may accompany diarrhea and dehydration.

## Objective Symptoms

### 1. **Skin:**

- Disseminated edematous rash evolves concomitantly with marked viraemia during the prodromal period. For smallpox, the rash follows 2-4 days after the onset of fever.
- Papular eruptions are typically distributed on the face and trunk.
- Papules evolve into vesicles, pustules, and crust over within 14-21 days. Skin lesions may vary in size like chickenpox, but develop in stages like smallpox.
- Crusting of the lesions begins over the last week (third) of illness. Central focus of crusts may be hemorrhagic with erythematous flares.

### 2. **Lymphadenopathy:** Pronounced generalized lymphadenopathy.

### 3. **Mucous membranes:** Ulcerated, possibly necrotic lesions within the oropharynx may occur.

### 4. **Systemic reactions:** Secondary complications of bacterial infection, bronchopneumonia, and pulmonary distress have been more frequently described for primary human cases of infection acquired from an animal source than those attributed to a presumed human source. The development of toxemia, so prevalent with human smallpox, has not been observed for human monkeypox infections.

## Differential Diagnosis

Monkeypox has often been misdiagnosed as smallpox, chickenpox, or a non-specific bacterial infection. A more severe infection may present in persons with compromised or suppressed immune systems. Monkeypox in healthy persons may resemble *molloscum contagiosum* infection, an opportunistic disease most often seen in patients suffering from HIV/AIDS.

- **Time and pattern of appearance:** The pronounced, acute swelling of the lymph nodes in monkeypox patients occurs shortly before the rash. The skin lesions appear and evolve and mature at the same stage as smallpox.
- **Density and location:** Monkeypox lesions may have either a chickenpox-like distribution (most common) or a smallpox-like distribution, including on the hands and feet. Smallpox lesions are densest over the face and extremities and uniform in size.
- **Physiology:** Monkeypox lesions are deep like smallpox, which can leave pitted scars. Monkeypox pitted scarring can resolve, unlike those left by smallpox.



**Figure 1: Comparison of Smallpox and Monkeypox infections.** Monkeypox infection (left) and smallpox (right). Note the pronounced enlargement of the inguinal lymph nodes in the monkeypox case. The distribution and severity of the rash for both diseases is also different.

## **Diagnostic Samples and Related Biosafety Issues**

Clinical examination of the patient during the onset of fever is the most important first step for confirming a case of monkeypox infection. The clinician or medical technician with a recent history of vaccination should always perform specimen collection for laboratory analysis. Throat cultures for virus can be obtained using a cotton swab; lesions can be scraped using the blunt edge of a scalpel to collect fluid. Scabs can be picked off with forceps. Specimens should be deposited in a primary sterile vacutainer tube sealed with tape, and packaged according to International Air Transport Association (IATA) and/or U.S. Department of Transportation (DOT) regulations. State and local health authorities should be immediately contacted before specimens are shipped.

Laboratory examination and diagnosis requires Biosafety Level-3 containment facilities where appropriately trained personnel and equipment are available.

Monkeypox infection can be confirmed in the laboratory by electron microscopic examination of vesicle fluid and tissue or serum. Definitive laboratory identification involves replication of the virus in cell culture (Vero cells) or on the chorioallantoic membrane of 11 day-old embryonated specific pathogen-free (SPF) chicken eggs, polymerase chain reaction (PCR), restriction fragment-length polymorphism (PFLP) analysis, or examination by electron microscopy.

## **Protection, Isolation and Notification**

The discovery of a case of human monkeypox should be treated with care and caution. Federal, state, and local health officials should be immediately notified so that the appropriate public health resources can be activated. Exposures that are suspected to have originated from an animal vector should be immediately reported to state and local health services.

Upon laboratory confirmation of a case of human monkeypox infection, all potential patient contacts should be notified, vaccinated, and placed under surveillance. Additional contacts presenting with prodrome should be vaccinated and quarantined at home under observation for 17 days. Persons developing fulminate disease should be quarantined for a minimum of 21 days, or until the scabs separate. Respiratory and contact precautions should be judiciously exercised throughout the course of infection particularly with persons that may present with bronchiolitis/ bronchopneumonia or viral pneumonia.

### **Public Health Notification Requirements**

According to the Centers for Disease Control and Prevention's (CDC) Preparedness protocols, all suspected monkeypox cases should be reported to state and local health departments. These agencies, in turn, will notify the CDC and conduct a formal investigation. Laboratory confirmation and interpretation of samples can be submitted to the CDC with prior coordination. Please visit the CDC Website for additional information, city and county health department contact information, as well as emergency hotline numbers <http://www.cdc.gov/ncidod/monkeypox/index.htm>.

## Vaccination and Post-Exposure Prophylaxis and Treatment

The current preparation of calf lymph- derived smallpox vaccine has been administered to tens-of-millions of people worldwide since the early 1960's. A similar vaccine derived from cell culture is in production. Similar contraindications for vaccination described for smallpox preservation are appropriate to follow suspected or confirmed cases of monkeypox infection. Contraindications include 1) immunosuppression, 2) HIV/AIDS infection, 3) history or evidence of eczema, 4) heart conditions, and 5) pregnancy. The risk of developing monkeypox disease after a known or suspected exposure far outweighs the risks posed by vaccination. If available, vaccinia immune globulin (VIG) can be given concurrently with vaccination to persons with contraindications. VIG alone will most likely not prevent or attenuate monkeypox infection.

Vaccination administered before the onset of prodrome may provide protection against disease, reduce the severity of infection, or prevent death. Cidofovir, an FDA approved drug used to treat the symptoms of cytomegalovirus (CMV) infection of the eyes (CMV retinitis) in patients with AIDS, may prove useful in preventing monkeypox infection if administered beginning 1-7 days following an exposure but before patients become symptomatic. Cidofovir has shown anti-viral activity in rodents and non-human primates experimentally challenged by various routes of exposure with high doses of several *Orthopoxviruses* (i.e. cowpox, variola, and vaccinia viruses) by either prolonging the mean time-to-death (MTD) or preventing death, if administered before the onset of symptoms. Currently, there is insufficient evidence to indicate if cidofovir is more effective than vaccination. The drawbacks of cidofovir treatment are a requirement for intravenous (IV) infusion combined with pre-hydration; nephrotoxicity has been a reported complication. Secondary bacterial infection can be treated with antibiotics.

For detailed information about vaccine contraindications and screening visit the Centers for Disease Control and Prevention (CDC) webpage  
[http://www.cdc.gov/ncidod/monkeypox/smallpoxvaccine\\_mpox.htm](http://www.cdc.gov/ncidod/monkeypox/smallpoxvaccine_mpox.htm).

## Sources of Additional Information

- The Centers for Disease Control and Prevention Home Page  
<http://www.cdc.gov/ncidod/monkeypox/>
- The World Health Organization Website, search keyword “monkeypox”  
<http://www.who.int>
- The Marshfield Clinic Research Foundation Monkeypox webpage  
<http://research.marshfieldclinic.org/crc/monkeypox.asp>

<http://www.nlm.nih.gov/medlineplus/monkeypoxvirusinfections.html>  
<http://www.in.gov/isdh/healthinfo/monkeypox/>  
[http://www.dhfs.state.wi.us/dph\\_bcd/monkeypox/](http://www.dhfs.state.wi.us/dph_bcd/monkeypox/)  
<http://www.nlm.nih.gov/medlineplus/monkeypoxvirusinfections.html>  
<http://www.fda.gov/oc/opacom/hottopics/monkeypox.html>  
<http://www.health.state.mn.us/divs/idepc/diseases/monkeypox/>  
[http://www.stanford.edu/group/virus/pox/2000/monkeypox\\_virus.html](http://www.stanford.edu/group/virus/pox/2000/monkeypox_virus.html)  
<http://mslive.sonicfoundry.com/monkeypoxpr/index.asp>

## References:

Breman JG, Henderson DA, “Poxvirus dilemmas – monkeypox, smallpox, and biological terrorism” *NE J Med* 339(8): 556-559, 1998.

Breman JG. 2000. Chapter 5: Monkeypox: an emerging infection for humans? In: *Emerging Infections* 4. Ed. WM Scheld, WA Craig, JM Hughes. ASM Press, Washington, DC. 45-67.

Douglass NJ, Dumbell KR, “Independent evolution of monkeypox and variola viruses” *J Virol* 66(12): 7565-7567, 1992.

Douglass NJ, Dumbell KR, “DNA sequence variation as a clue to the phylogenesi of orthopoxviruses” *J Gen Virol* 77: 947-951, 1996.

Esposito JJ, Obijeski JF, et. al, “Serological relatedness of monkeypox, variola, and vaccinia viruses” *J Med Virol* 1: 35-47, 1977.

Esposito JJ, Nakano JH, et. al, “Can variola-like viruses be derived from monkeypox virus? An investigation based on DNA mapping” *Bull WHO* 63(4): 695-703, 1985.

Fenner F, et al. *Smallpox and its eradication*. Geneva, World Health Organization, 1988.

Fine PE, Jezek Z, et. al, “The transmission potential of monkeypox virus in human populations” *Int J Epidem* 17(3): 643-650, 1988.

Hahon N, Wilson BJ, “Pathogenesis of variola in *Macaca irus* monkeys” *Am J Hyg* 71: 69-80, 1960.

Hahon N, McGavran MH, “Air-borne infectivity of the variola-vaccinia group of poxviruses for the cynomolgus monkey, *Macaca irus*” *J Infect Dis* 109: 294-298, 1961.

Jahrling PB, Hensley L, et. al, “Lethal infection of primates with variola virus as a model for human smallpox” WHO, 9 Sep 2003.

<http://www.who.int/csr/disease/smallpox/lethalinfection/en/print/html>

Jezek Z, Grab B, et. al, “Clinico-epidemiological features of monkeypox patients with an animal or human source of infection” *Bull WHO* 66(4): 459-464, 1988.

Knipe DM, Howley PM (Ed.), *Fields Virology*, 4<sup>th</sup> ed., Washington, DC; Lippincott Williams and Wilkins, 2001: 2849-2921.

Lancaster MC, Boulter EA, et. al, “Experimental respiratory infection with poxviruses, II: Pathological studies” *Br J Exp Pathol* 47:466-471, 1966.

Loparev VN, Massung RF, et. al, "Detection and differentiation of old world orthopoxviruses: Restriction fragment length polymorphism of the *crmB* gene region" J Clin Microbiol 39(1): 94-100, 2001.

Meyer H, Ropp SL, et. al, "Gene for A-type inclusion body protein is useful for a polymerase chain reaction assay to differentiate orthopoxviruses" J Virol Meth 64: 217-221, 1997.

Richardson M, Dumbell RK, "Comparison of monkeypox viruses from animal and human infection in Zaire" Trop Geogr Med 46(5):327-329, 1994.

Strauss JH, Strauss EG. 2002. Chapter 6: DNA-Containing Viruses. In: Viruses and Human Disease. Academic Press, San Diego, CA. 223-233.

Westwood JCN, et al. Experimental respiratory infection with poxviruses. Br J Exp Pathol 47:453-465, 1966

Zaucha GM, Jahrling PB, et. al, "The pathology of experimental aerosolized monkeypox virus infection in cynomolgus monkeys (*Macaca fascicularis*)" Lab Invest 81(12): 1581-1600, 2001.

#### **On-Line References:**

"Monkeypox infections in animals: Interim guidance for veterinarians and pet owners" CDC, 9 Jun 2003. <http://www.cdc.gov/ncidod/monkeypox/animalguidance.htm>

"Update: Multi-state outbreak of monkeypox – Illinois, Indiana, Kansas, Missouri, Ohio, and Wisconsin, 2003" MMWR 52(25); 589-590, 27 Jun 2003.

"Updated interim case definition for human case of monkeypox" CDC, 2 Jul 2003. <http://www.cdc.gov/ncidod/monkeypox/casedefinition.htm>