Monkeypox

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Importance

Monkeypox (also known as mpox) is a zoonotic viral disease, endemic in western and central Africa, which circulates in wild animal hosts and emerges periodically to affect humans, captive or wild nonhuman primates, and other species, particularly rodents. Congo Basin monkeypox viruses are particularly virulent, with human case fatality rates during outbreaks in parts of Africa estimated to be around 10%. West African viruses tend to cause milder disease; however, deaths are seen occasionally in young children, individuals with secondary bacterial sepsis or rare complications such as encephalitis, and people who are immunosuppressed.

Monkeypox outbreaks have been reported sporadically in nonhuman primate facilities around the world, especially in the past. Human cases are almost always seen in Africa, but a large outbreak in Nigeria in 2017-2018 resulted in a few imported cases among travelers to Europe and Asia, with one case resulting in person-to-person transmission to a hospital worker. One outbreak occurred in the United States in 2003, associated with virus transmission between exotic pets and from pets in humans. A prompt diagnosis of imported monkeypox can help prevent this disease from becoming established outside Africa in potential animal reservoirs, such as prairie dogs or released exotic pets.

Etiology

Monkeypox results from infection by monkeypox virus, a member of the genus *Orthopoxvirus* in the family Poxviridae (subfamily Chordopoxvirinae). Two viral clades, the West African (clade II) and Congo Basin (clade I) clades, have been identified. The Congo Basin viruses are more virulent. Monkeypox virus is closely related to some other orthopoxviruses including variola (smallpox) virus, and it cannot be distinguished from these viruses in some laboratory tests.

Monkeypox should not be confused with benign epidermal monkeypox (BEMP), a poxviral disease of primates caused by tanapox virus, an antigenically unrelated virus in the genus *Yatapoxvirus* of the family Poxviridae.

Species Affected

The monkeypox virus's full host range is uncertain. Animals known to be susceptible to infection include diverse Old and New World monkeys and apes, and various rodents, shrews and other small mammals, as well as dogs. Among nonhuman primates, clinical cases have been described in chimpanzees (*Pan troglodytes*) and an infant sooty mangabey (*Cercocebus atys*) in the wild, as well as captive gorillas (*Gorilla gorilla*), chimpanzees, Asian orangutans (*Pongo pygmaeus*), gibbons (*Hylobates lar*), marmosets (*Hapale jacchus*), and various monkeys in the genera *Cercopithecus*, *Macaca* and *Siamiri*. Antibodies have been found in other wild or captive nonhuman primates.

During the 2003 outbreak in the U.S. associated with exotic pets, infected animals included Gambian giant pouched rats (*Cricetomys* spp.), North American black-tailed prairie dogs (*Cynomys ludovicianus*) rope squirrels (*Funisciurus* spp.), dormice (*Graphiurus* sp.), a groundhog/ woodchuck (*Marmota monax*), an African hedgehog (*Atelerix* sp.), a jerboa (*Jaculus* sp.) and two opossums (*Didelphis marsupialis* and *Monodelphis domestica*). Chinchillas (*Chinchilla lanigera*) and coatimundis (*Nasua nasua*) developed antibodies after exposure, but viral DNA or infectious virus was not found. Giant anteaters (*Myrmecophaga tridactyla*) were thought to have been involved in an outbreak among primates at the Rotterdam Zoo in the Netherlands in 1964. Limited early surveillance in sheep, goats and cats in Africa found no evidence of exposure, but antibodies were detected in one pig. A subsequent attempt to infect pigs by rubbing virus into the skin did not result in virus recovery except from the inoculation site. One case was reported in a dog during the 2022 outbreak, apparently acquired during close contact with humans in the household. Experimental infections with clinical signs have also been reported in 13-lined ground squirrels (*Spermophilus tridecemlineatus*), the cotton rat (*Sigmodon hispidus*), forest giant squirrel (*Protexerus strangeri*), bobak marmot (*Marmota bobak*), and red squirrels (*Sciurus vulgaris*). Adult

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white rabbits (with the apparent exception of albino rabbits), guinea pigs, white rats (*Rattus* spp.) and wild type laboratory mice (*Mus musculus*) are refractory to experimental infection, though newborn rats and rabbits can be infected.

The reservoir host(s) for monkeypox viruses are uncertain, but are thought to be one or more African rodents or small mammals. It is possible that the Congo Basin and West African clades are maintained in different species. Two genera of African squirrels, *Funisciurus* spp. (rope squirrels) and *Heliosciurus* spp. (sun squirrels), are among the top candidates for reservoir hosts, but antibodies have also been found in many other species of African rodents, shrews and other small mammals including Gambian pouched rats. Attempts to detect the virus directly in wild small mammals or other free-living species have generally been unsuccessful, though it was recovered once from a wild rope squirrel with lesions.

Zoonotic potential

The Congo Basin and West African clades of monkeypox virus can both affect humans.

Geographic Distribution

Monkeypox is endemic in central Africa (the Congo Basin) and West Africa. An outbreak of monkeypox affecting humans and exotic pets occurred in the U.S. in 2003, but there is no evidence that the virus became established in North America. Isolated human cases were recently imported to other locations, including the U.K., Israel and Singapore, again without the virus becoming established in these locations.

Transmission

Monkeypox viruses has been found in skin lesions and most or all secretions and excretions (e.g., urine, feces, and oral, nasal and conjunctival exudates) in animals. Likely routes of transmission include inhalation, direct inoculation into breaks in the skin, and the ingestion of infected tissues. The importance of aerosol transmission might differ between species or situations. Experimentally infected prairie dogs can shed monkeypox viruses until 21 days after inoculation, and limited evidence suggests that some small animals, such as dormice and Gambian giant pouched rats, might carry this virus for a few weeks or months. Viral DNA was detected in the tissues, urine and feces of one dormouse for at least 6 months, but no viral antigens were found when this animal was euthanized. Whether such animals can shed infectious virus is not known.

Humans can become infected via bites from animals, in aerosols during close contact, or by direct contact with lesions, blood or body fluids. Sexual transmission was suspected in a few cases, when there were lesions on the genitalia, and transplacental transmission has been documented. In Africa, clinical cases have often been linked to handling, preparing and eating wild animals, but person-to-person transmission was also significant in some outbreaks. In the U.S., most cases occurred among people who had close direct contact with prairie dogs; some infections were apparently acquired in scratches and bites, or through open wounds. Monkeypox virus has been isolated from humans for up to 18 days after the onset of the rash, and scabs shed during recovery were found to contain significant amounts of infectious virus. Person-to-person transmission does not seem to be capable of maintaining the virus in human populations.

Disinfection

Disinfectants reported to be effective for orthopoxviruses include sodium hypochlorite, chloro-xylenol-based household disinfectants, glutaraldehyde, formaldehyde and paraformaldehyde. During an outbreak in the U.S., the U.S. Centers for Disease Control and Prevention (CDC) recommended 0.5% sodium hypochlorite or other EPA–approved high–level disinfectants. Incineration or autoclaving is appropriate for some contaminated materials.

Infections in Animals

Incubation Period

Reported incubation periods in experimentally infected animals range from 3 days to about 2 weeks in most cases. The incubation period was slightly longer (11 to 18 days) in prairie dogs infected by exposure to fomites than after direct exposure.

Clinical Signs

Nonhuman primates

The predominant syndrome in nonhuman primates is a self–limited rash, which begins as small cutaneous papules that develop into pustules, then crust over, and may leave small scars when the crusts drop off. A typical monkeypox lesion has a red, necrotic, depressed center, surrounded by epidermal hyperplasia. The number of lesions varies from a few individual pocks to extensive, coalescing lesions. They sometimes affect the entire body, but may be more common on the face, limbs, palms, soles and tail. Some animals have only skin lesions, which may be accompanied by a fever or lymphadenopathy, but do not appear to be otherwise ill. In more severe cases, there may also be respiratory signs (coughing, nasal discharge, dyspnea), ocular discharge, anorexia, facial edema or oral ulcers. Respiratory signs of varying severity, with minimal skin lesions (e.g., a single lesion on the lip), were observed in some wild chimpanzees during an outbreak caused by a West African virus. Other animals in this outbreak had more classical signs including a rash. Most naturally infected animals recover; however, fatalities are sometimes seen, particularly in infant monkeys. Asymptomatic infections are also possible.

Prairie dogs and other species

In prairie dogs, the clinical signs may include fever, depression, anorexia, blepharoconjunctivitis (often the initial sign), respiratory signs (nasal discharge, sneezing and/or coughing, respiratory distress), diarrhea, skin lesions similar

to those in nonhuman primates, and oral ulcers. Lymphadenopathy was seen in naturally infected prairie dogs, but did not occur in all experimentally infected animals. Elevated serum levels of liver enzymes have also been reported. Some cases are fatal, and experimentally infected prairie dogs sometimes died without developing lesions on the skin or mucous membranes.

Similar clinical signs have been reported in other naturally or experimentally infected rodents; however, not all animals developed skin lesions. Intranasally inoculated dormice, which often died, had only nonspecific signs such as lethargy, an unkempt hair coat, a hunched posture, conjunctivitis and dehydration. Some naturally infected Gambian giant pouched rats had asymptomatic infections or mild illnesses, with no respiratory signs and limited skin lesions, but other animals died, and experimentally infected pouched rats sometimes became moderately to severely ill, with skin and oral lesions, ocular lesions and nonspecific signs of illness. Pox lesions were found in a wild Thomas's rope squirrel (*Funisciurus anerythrus*) in Africa that was found infected with a Congo Basin strain. Some rope squirrels (*Funisciurus anerythrus*) inoculated with a Congo Basin strain developed skin and oral lesions, respiratory signs and, in one case, corneal lesions. However, African squirrels administered a high viral dose in an earlier study died with a generalized, nonspecific illness, and skin lesions occurred only in a few animals that received a lower, nonfatal dose.

A case in a healthy greyhound dog was characterized by skin and mucosal lesions that included slightly crusty, erythematous pustules on the abdomen and a small erosion on the anus. Viral nucleic acids were also detected in oral secretions by PCR. Systemic signs were not described in this animal.

Post Mortem Lesions

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At necropsy, the skin may contain one or more papules, umbilicated pustules ("pocks") with central necrosis, or crusts over healing lesions. Ulcers, erosions or lesions with necrotic centers may be found in the mouth of some animals. Peripheral lymphadenopathy is common but not always present. Conjunctivitis or blepharoconjunctivitis may also be noted.

Pox lesions (white plaques or small, white, firm, deeply embedded foci with umbilicated necrotic centers) are sometimes detected on internal organs or in the stomach and small intestine. Some animals may have other internal lesions including lung involvement (e.g., pleuritis, consolidation of the lung, pulmonary edema, multifocal necrotizing pneumonitis or bronchoalveolar pneumonia), enlargement and/or mottling of the liver, orchitis, and multifocal necrotizing lesions in various organs and tissues including the spleen, liver, colon, thymus, brown fat, uterus or vagina. Hemorrhages were noted in the upper gastrointestinal tract, nasal cavity, gall bladder and brain of intranasally inoculated dormice, and in the lungs of experimentally infected ground squirrels, together with pulmonary edema.

Diagnostic Tests

The characteristic skin lesions and histopathology are suggestive, but can be caused by other diseases. If the animal has not been exposed to other orthopoxviruses, monkeypox can be tentatively diagnosed by detecting orthopoxvirus virions with electron microscopy or orthopoxvirus antigens by immunohistochemistry.

The diagnosis can be confirmed by virus isolation or assays for genetic material, such as PCR. Monkeypox virus may be detected in skin lesions or samples from affected organs at necropsy, and sometimes in conjunctival swabs or oral and nasal secretions (e.g., oropharyngeal swabs). One study found that the liver contained particularly large amounts of virus in dormice. The virus has also been detected in the blood, urine and/or feces of some animals. Monkeypox virus can be recovered in various cell lines including Vero cells, and may be specifically identified with PCR followed by restriction fragment–length polymorphism (RFLP) analysis or sequencing. Monkeypox-specific PCR assays are available in some laboratories, and a DNA oligonucleotide microarray can identify this virus rapidly and specifically. PCR can also be performed directly on clinical samples. Loop-mediated isothermal amplification (LAMP) assays for the Congo Basin and West African strains have been developed. Serology is mainly used for surveillance in animals. Antibodies to other orthopoxviruses can cross-react with monkeypox virus.

Treatment

Treatment is supportive, but may not be advisable or allowed in some situations. During the 2003 outbreak in the U.S., the CDC recommended that all animals with suspected monkeypox be euthanized, in part to prevent zoonotic infections. Nonhuman primates are not necessarily euthanized during outbreaks in facilities.

Control

Disease reporting

Veterinarians who encounter or suspect monkeypox should follow their national and/or local guidelines for disease reporting. In the U.S., state or federal authorities must be notified immediately.

Prevention

As a result of a monkeypox outbreak in 2003 that was caused by imported exotic pets, the U.S. banned the importation of six types of African rodents – squirrels in the genera *Heliosciurus* and *Funisciurus*, dormice, Gambian giant pouched rats, brush-tailed porcupines (*Atherurus* sp.), and striped mice (*Hybomys* sp.). This ban applies to these animals whether they were born in Africa or on another continent. In addition, prairie dogs can no longer be captured from the wild for use as pets. Exceptions to these restrictions are allowed, by permit, for organizations such as zoos and scientific institutions. Similarly, some other countries and governing bodies such as the E.U. banned the importation of prairie dogs from the U.S. and some rodents from Africa.

Good infection control measures, including the isolation of new animals, help prevent outbreaks in primate facilities and facilities that import exotic pets. Because infections have been reported in Asian monkeys mixed with primates from Africa, these species should not be housed in the same area. Care should be taken to avoid spreading the virus on fomites. Vaccination with vaccinia virus (smallpox vaccine) is protective in nonhuman primates. Research suggests this vaccine is also protective in some other species such as prairie dogs. Anyone who has been exposed to monkeypox should avoid contact with animals that might be susceptible to infection, particularly rodents and nonhuman primates.

Morbidity and Mortality

A few outbreaks have been reported among captive primates, but the only cases observed in wild species were in an infant sooty mangabey found dead with pox lesions and an outbreak in a group of monitored chimpanzees in 2017-2018. Based on these reports, both published recently, and a study that found antibodies in 8% of nonhuman primates in Africa, it appears likely that some clinical cases in wild primates are missed. The morbidity rate in nonhuman primates is usually high and the mortality rate low, with most adult animals recovering. More severe illnesses may be seen in infants, which sometimes die, and primates of all ages infected experimentally via aerosols. There also seem to be species-related differences in susceptibility. Crab-eating macaques (*Macaca fascicularis*) appear to be more susceptible than rhesus macaques (*M. mulatta*), and 6 of 9 captive Asian orangutans (*Pongo pygmaeus*) died in an outbreak at the Rotterdam zoo while two gorillas and most chimpanzees survived despite becoming ill.

As of 2020, only a single clinical case has been described in a wild rodent in Africa, a squirrel (*Funisciurus anerythrus*) with poxvirus lesions. However, antibodies are reported regularly in African squirrels of the genera *Funisciurus* and *Heliosciurus*, and high seroprevalence rates have sometimes been found in other species, such as Natal multimammate mice (*Mastomys natalensis*), tiny fat mice (*Steatomys parvus*) and shrews (*Crocidura* spp.) in Zambia. Prairie dogs seem to be very susceptible to monkeypox. Many of the prairie dogs exposed to monkeypox became infected during the outbreak in the U.S., and mortality rates as high as 60% have been reported after experimental inoculation. Another study reported 50-75% mortality in rope squirrels (*Funisciurus anerythrus*) inoculated with a Congo Basin strain. However, some species of rodents might be relatively resistant to clinical signs. During the outbreak in the U.S., monkeypox virus was found in one Gambian giant pouched rat that died soon after arrival, but another animal had a very mild illness, and orthopoxvirus antibodies were found in 12 of 18 healthy individuals after the outbreak. Limited experimental evidence also suggests that Gambian pouched rats are less susceptible than rope squirrels or prairie dogs.

The Congo Basin clade seems to be more virulent than West African viruses for nonhuman primates and some rodents (e.g., prairie dogs, squirrels), although a West African virus was reported to be at least as virulent for Gambian pouched rat as the Congo Basin strain.

Infections in Humans

Incubation Period

Reported incubation periods in humans range from 7 to 24 days, with a mean of 12 days in Africa and 14.5 days during the outbreak in the U.S.

Clinical Signs

Human monkeypox resembles smallpox, with a rash and constitutional signs, but the symptoms are generally milder and, unlike smallpox, the lymph nodes are usually (though not always) enlarged. Most often, the illness begins with nonspecific, flu–like symptoms that may include malaise, fever, chills, headache, sore throat, myalgia, backache, fatigue, nausea, vomiting and a nonproductive cough. Lymphadenopathy can be regional or generalized, and most often affects the submandibular, postauricular, cervical and/or inguinal lymph nodes.

Most patients develop a rash one to several days after they begin to feel ill, though there have been instances where patients noticed a few skin lesions (e.g., at the site of an animal bite or scratch, or in the groin) shortly before they felt unwell. Skin lesions are usually concentrated on the extremities (including the palms and soles), but they can also be seen on the head and torso, as well as the mucous membranes and genitalia. They vary in number from less than 25 to more than a hundred, and may become confluent in severe cases. As in animals, skin lesions usually begin as macules and papules, which develop into vesicles and pustules ("pocks"), umbilicate, form scabs and are eventually shed. During the outbreak in the U.S., some pustules had prominent erythematous flares. Such flares have not been noted in African cases, possibly because most affected people have darker skin. The skin lesions usually resolve within 14 to 21 days. Residual varioliform scarring, with hypopigmented and/or hyperpigmented skin lesions, may be a sequela in some cases. Severe scarring, as seen in smallpox, is rare.

Some patients also have ocular signs including conjunctivitis, or more rarely, keratitis or corneal ulceration. Respiratory complications including bronchopneumonia, coagulation disorders, and rare cases of encephalitis or multiorgan failure have also been reported. Secondary bacterial infections can occur, and may lead to sepsis. Pregnant women may abort or give birth to an infected fetus. One fetus infected *in utero* was stillborn, with cutaneous maculopapular skin lesions and severe hepatic involvement; another had skin lesions and was born prematurely but alive. At least one mildly affected pregnant woman gave birth to a full-term, healthy child. Most patients recover in 2-4 weeks, but deaths are possible, especially in people infected with the Congo Basin clade or immunosuppressed individuals infected with either clade. Subclinical and very mild cases have also been reported.

Diagnostic Tests

Monkeypox can be tentatively diagnosed if the characteristic skin lesions are present and there is a history of exposure; however, clinical cases can resemble chickenpox and may be difficult to distinguish clinically from the latter disease. Tests to isolate monkeypox virus or identify its nucleic acids and antigens are similar to those used in animals. At least one rapid point-of-care test, a lateral flow assay for viral antigen, is commercially available. In humans, monkeypox virus can be found in skin lesions (e.g., in scabs or material from vesicles) or throat and nasopharyngeal swabs.

Serology may be helpful in some cases, although cross-reactions with other orthopoxviruses complicate the interpretation of serological tests. An enzyme-linked immunosorbent assay (ELISA) can be used to detect orthopoxvirus-specific IgM. A rising IgG titer in paired samples is also suggestive. Cross-adsorbed virus neutralization, immunofluorescence or hemagglutination inhibition assays, as well as immunoblotting (Western blotting), can be used to distinguish reactions to monkeypox virus and smallpox virus, although some of these assays are not always easy to interpret. A specific ELISA that may detect monkeypox antibodies in people vaccinated for smallpox has been reported in the literature.

Treatment

Treatment of monkeypox is mainly supportive. Tecovirimat (chemical agent ST-246), which is also known as Arestyvir, has been licensed for use in humans infected with orthopoxviruses, but its specific efficacy against monkeypox in people has not yet been evaluated. Other possible agents, including a derivative of cidofovir (CMX001/ Brincidofovir) are in clinical trials. Vaccinia immune globulin, which was used at one time to treat smallpox, might also be tried, especially in those who are immunocompromised.

Prevention

Smallpox (vaccinia) vaccination appears to provide some protection from monkeypox, and it has been recommended for some healthy people in occupations at high risk of exposure. Post–exposure vaccination also seems to be helpful, and may be offered to people who are exposed to a monkeypox-infected person or animal. This vaccine cannot be used in those who are immunocompromised. The general population is not currently vaccinated in endemic areas of Africa, due to the expense of the vaccine and the risk of serious side effects, particularly in areas where undiagnosed severe T cell immunodeficiencies (e.g., untreated HIV-1 infection) may be relatively common. A vaccine specifically for monkeypox is in clinical trials in Africa, as of 2020.

As a routine preventive measure, care should be taken to treat and cover breaks in the skin when working with nonhuman primates or other animals that may be hosts for monkeypox virus. Infection control procedures such as good hygiene, frequent hand washing, disinfection of surfaces and equipment, and the use of personal protective equipment (PPE) are important during contact with animals suspected to have monkeypox. Necropsies should be done in Biosafety Level 2 laboratories, using a certified Class II Biological Safety Cabinet. Anyone who has been in contact with a monkeypox suspect should contact a health care provider immediately. Health authorities (e.g., the local or state health department) must also be informed.

Isolation of infected patients and good infection control measures are helpful in preventing person-to-person transmission. Ring vaccination might also be used in some outbreaks. Because the full host range of monkeypox virus is uncertain, infected individuals should also limit their contact with any pet, particularly species known to be susceptible to this virus.

Morbidity and Mortality

In Africa, monkeypox is usually seen in rural populations, and is most common in children and young adults. Most cases occur among people who live in or near heavily forested areas, where the virus is thought to be endemic in animals, though outbreaks have been reported elsewhere. Clinical cases often occur after contact with wild small mammals, which are caught for food and other purposes, but person-to-person transmission and family clusters appear to be significant in some outbreaks. In the past, monkeypox was thought to be a rare disease; however, outbreaks and sporadic cases have increasingly been reported from Africa during the last few decades. Waning immunity from smallpox vaccinations may be a factor, as the disease predominantly affects young people born after vaccination campaigns ended. Other societal factors (e.g., changes resulting from poverty or war) that increase exposure to the reservoir hosts are also plausible, as are some impacts from increased awareness and reporting.

Most outbreaks have occurred in central Africa and are caused by the Congo Basin clade, which is more virulent. Until recently, clinical cases caused by the West African clade were seen only rarely. The first significant outbreak in recent years occurred in 2003 in the U.S. and was linked to imported exotic pets, which disseminated the virus to pet prairie dogs and hence to humans. Seventy-two human infections were reported, including 37 that were laboratory confirmed. Most cases occurred after direct contact with pet prairie dogs. African rodents appeared less likely to transmit the disease to humans, possibly due to different types of behavioral interactions with these animals. In 2017-2018, a West African virus caused at least 132 confirmed and approximately 300 suspected cases in Nigeria. This event, the first significant outbreak in Nigeria since the 1970s, occurred after floods that may have increased human exposure to rodents. Many cases appeared to result from person-to-person propagation of the virus. Since then, increased surveillance has uncovered sporadic, ongoing human cases in Nigeria. Serological surveillance has also revealed antibodies to orthopoxviruses in some healthy

young people in West Africa who report no previous illness suggestive of monkeypox.

The highest risk of death from monkeypox is in infants, young children and immunocompromised individuals. Reported case fatality rates in outbreaks caused by Congo Basin (Central African) strains reach 10% or more, and are occasionally as high as 20-25% in some smaller clusters. However, there is still uncertainty in these estimates, as milder cases might be missed and co-morbidities are common in affected areas. Clinical cases caused by West African clade viruses seem to be milder. No deaths occurred during the outbreaks in the U.S., while 7 deaths were seen in the recent outbreak in Nigeria. Four of these fatalities occurred in immunocompromised individuals, two of whom had uncontrolled HIV-1 infections. One case of encephalitis and bronchopneumonia was fatal in a neonate, and two HIV-negative adults died with bronchopneumonia and sepsis. Although secondary bacterial infections were relatively common in this outbreak, other serious complications such as encephalitis, keratitis or bronchopneumonia were rare in both this outbreak and the 2003 outbreak in the U.S. The availability of advanced health care facilities and good supportive care, as well as the absence of poor nutrition and concurrent diseases, may contribute to higher survival rates for monkeypox in some areas.

Internet Resources

Centers for Disease Control and Prevention (CDC). Monkeypox

European Centre for Disease Prevention and Control (ECDC). Monkeypox

Public Health Agency of Canada. Pathogen Safety Data Sheets

The Merck Manual

The Merck Veterinary Manual

Wisconsin National Primate Research Center (WNPRC), University of Wisconsin

World Health Organization. Monkeypox

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