



Monkeypox: considerations for the understanding and containment of the current outbreak in non-endemic countries

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Abstract The neglected and rare zoonotic disease caused by monkeypox virus (MPV) has recently spread widely, resulting in the largest known monkeypox outbreak outside of Africa, where it is endemic. MPV belongs to the *Poxviridae* family, genus *Orthopoxvirus*. At least two different clades have been identified, each having different fatality rates but recent cases are all phylogenetically related to the West African clade. MPV is transmitted directly by either person-to-person, -animal, or virus-contaminated fomite contact. The disease is often self-limited, and clinical symptoms include fever, skin lesions, and lymphadenopathies. At present, no deaths have been associated

with the current outbreak. MPV DNA detection using molecular techniques is recommended for diagnosis. At least two approved drugs for antiviral therapy are available in the USA. Two different vaccines, including the vaccine used in the past for smallpox eradication and a new formulation more recently approved based on a live but non-replicating virus, are available that provide immunity to MPV. These and other clinical and public health considerations pertaining to the recent monkeypox outbreaks together with aspects of MPV biology are discussed in this article.

Keywords Monkeypox · Outbreak · *Orthopoxvirus* · Epidemiology · Diagnosis · Clinical presentation · Prophylaxis · Antiviral therapy

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Introduction

Monkeypox is a neglected infection that causes small outbreaks in different communities in West and Central Africa. There, zoonotic spillover and anthropogenic factors converge to favor its periodic re-emergence. This is evidenced by the fact that trade-in rodents have inadvertently exported monkeypox to the USA in 2003 and when six human travelers from Nigeria exported the disease to Israel, Singapore, and the UK in 2018–2019 [1–4]. In July 2021, a man who traveled from Lagos, Nigeria, to Dallas, TX (USA), became the seventh itinerant to a non-African country with diagnosed monkeypox [5].

On May 4, 2022, a traveler who returned from Nigeria was confirmed as the first case in the UK. Thereafter, other unrelated cases were detected to date in five different continents, suggesting that there may have been multiple introductions from Africa. This outbreak is expanding, currently involving at least 47 countries that have informed the sudden appearance of more than 1600 confirmed cases of monkeypox virus (MPV) infections [6]. These events have triggered a coordinated response in the public health community across the globe. Smallpox was one of the most devastating diseases that could potentially be used as a biological weapon produced by the variola virus, a member of the *Orthopoxvirus* genus. While monkeypox infection can cause illness clinically indistinguishable from smallpox, it is thought to spread slowly, reducing the chances for a widespread, rapidly expanding pandemic. The current outbreak is a peculiar and unsettling reminder of poxviruses, a largely forgotten threat since the last natural case of smallpox was recorded in Somalia in 1977 and the subsequent declaration of eradication from the World Health Organization (WHO) on 8 May 1980. From that moment, the World Health Assembly has trusted the preservation of viable variola virus to only two authorized facilities in Russia and the USA [7].

The interruption of smallpox vaccination—which can provide some cross-protection against monkeypox—resulted in an increasingly larger number of people that are vulnerable to infection by MPV or other *Orthopoxviruses*, leading to increased human-to-human transmission cases among young children and young adults that have spread out of Africa to other countries [8].

MPV was first reported in 1959 as an outbreak of smallpox-like disease in monkeys at a research institute in Copenhagen, Denmark [9]. The first human MPV case in medical history was recognized on September 1, 1970, when a 9-month-old child in the Democratic Republic of Congo was hospitalized with a smallpox-like illness from which an MPV-like virus was isolated [10]. In subsequent years, numerous other human cases were reported. From 1970 to 1999, WHO reported at least 404 confirmed and about 500 suspected human monkeypox cases in several African countries (Central African Republic, Cameroon, Nigeria, Côte d'Ivoire, Liberia, Sierra Leone, and Gabon), but mainly in the Democratic Republic of Congo [11, 12]. Since then, several thousand human

monkeypox cases have been confirmed in 15 different countries, 11 of which were in African countries. Since 2003, importation- and travel-related spread outside Africa has occasionally resulted in MPV outbreaks. Cases of people with febrile illness and rashes were reported in the USA, but there were no deaths, and no human-to-human transmission was detected. The source of this outbreak was found to be the importation of infected exotic animals from Ghana [13]. In the first four months of 2022, WHO reported 1238 and 46 new cases in the Democratic Republic of Congo and Nigeria, respectively [14].

Interactions with infected animals or individuals are risk behaviors associated with acquiring the infection. The spread of monkeypox beyond Africa underscores the global relevance of the disease and suggests that the reemergence of monkeypox in humans may fill the epidemiological niche vacated by smallpox. Increased surveillance and standardized diagnosis are critical tools to understand the ever-changing epidemiology of this reemerging disease.

The virus

General concepts and taxonomy

The *Poxviridae* is a large and diverse family of double-stranded DNA viruses whose entire life cycle occurs in the cytoplasm of infected cells. Poxviruses are known as brick-shaped or oval structures that measure 200–400 nm when viewed with an electron microscope [15]. This family includes 18 genera that infect vertebrates, but among them *Orthopoxvirus* is the most important and best characterized poxvirus genus, mainly because of their impact on human and animal health. They are primarily named after the hosts from which they were first isolated and identified. However, the name does not necessarily represent their natural reservoir or their complete host range, and to date, the primary hosts and reservoirs of zoonotic *Orthopoxviruses* in nature or their transmission and maintenance cycles are not fully defined [16].

Electron microscopic images show that poxviruses share common features in terms of size and shape. For example, the size of MPV virus particles ranges from 200 to 250 nm and appears as egg-shaped or brick-shaped particles enclosed by

a geometrically corrugated lipoprotein outer membrane [17]. Membrane junctions as well as the densely packed core containing enzymes, a double-stranded DNA genome, and transcription factors are protected by the outer membrane. Based on an electron microscopy fixation artifact, the core is described as biconcave and has a side body on each side. The MPV genome consists of a linear double-stranded DNA (≈ 197 kb) containing terminal inverted repeat sequences and hairpin termini and comprising several hundred closely spaced open reading frames [18]. The MPV genome encodes all proteins required for viral DNA replication, transcription, virion assembly, and egress. The genes encoding housekeeping functions are highly conserved among *Orthopoxviruses* and are located in the central region of the genome, whereas the genes encoding virus-host interactions are less conserved and are located in the termini region [19]. A comparison of the variola and MPV genomes reveals that the central region of the MPV genome encodes essential enzymes and structural proteins and is 96.3% identical to that of the variola virus. However, the end regions of the MPV genome that encode virulence and host range factors differ significantly. These are four regions of high variability in *Orthopoxvirus* in the regions around bases ~ 470 0; $\sim 175,100$; $\sim 184,000$; and $\sim 197,700$ (numbered according to AY603973). Thus, these two viruses appear to be distinct species that evolved independently from the *Orthopoxvirus* ancestors [20]. The classical neutralization or hemagglutination inhibition reaction does not allow differentiation between MPV and variola, but it can be performed with antisera directed against specific viral antigens. In addition, each *Orthopoxvirus* can be identified by analyzing its specific composition of surface epitopes, characteristic polypeptides, unique DNA cleavage sites, and specific differences in the long terminal repeats of the double-stranded DNA genome [21].

Monkeypox virus: clades and animal host-range

Monkeypox is considered the most important *Orthopoxvirus* infection in humans since the eradication of smallpox and its virus isolates are divided into two clades based on genetic and phenotypic differences, namely, the West African and Congo Basin clades. The Congo Basin strain kills up to 10% of

those infected, but the current outbreak appears to affect only the West African strain, which has had a mortality rate of about 1% in previous outbreaks [22, 23]. According to the WHO, all infected persons in the UK have contracted the West African clade of the virus. It is noteworthy that clinical signs are similar in infections caused by viruses of both clades [24]. Many infections occurred in sporadic clusters, suggesting “spillover” with limited subsequent human-to-human transmission. Nevertheless, the host range of *Orthopoxviruses* can be both highly specialized, host restricted, and generalist with a broad host range. For example, the variola virus is a highly specialized virus that infects only humans, whereas MPV and vaccinia virus are examples of zoonotic *Orthopoxviruses* that can infect multiple mammalian hosts and spread to humans. Unlike the variola virus, MPV has a broad host range [25] that has allowed it to maintain a reservoir in wildlife while sporadically causing disease in humans, which has prevented global eradication by vaccinating in humans. However, the natural source of MPV and its maintenance cycle in nature remain not completely elucidated. The virus has been isolated from different wild animals including non-human primates (orangutans, chimpanzees, sooty mangabeys, cynomolgus monkeys) and in a variety of rodents (mice, rabbits, squirrels, hamsters, groundhogs, and porcupines). In addition, susceptibility to MPV infection has been noted in anteaters, black-tailed prairie dogs, southern opossums, short-tailed opossums, marmosets, and African hedgehogs [26–29]. There is no available data about differences in the host-range between viral isolates belonging to Western African and Congo Basin clades.

Currently, a potential risk for reverse zoonotic transmission (human-to-animal transmission) is being monitored, as this could allow the virus to become established in wildlife, as is the case in Africa. New reservoirs of viruses would thus increase the likelihood of repeated transmission to humans. Therefore, it is important that rodents belonging to confirmed human disease cases be kept isolated and monitored to avoid possible transmission. In addition, despite the low risk for this phenomenon, such transmission may be silent because infected animals usually do not show the same visible symptoms as humans.

How infection spread

Monkeypox: routes of transmission

The two possible routes of MPV transmission are animal-human transmission and human–human transmission. Respiratory droplets and contact with body fluids, contaminated patient surroundings or objects, and skin lesions from an infected person have been found to be associated with human-to-human transmission. Monkeypox virus, which belongs to the Central African clade, is more susceptible to human-to-human transmission because it is more virulent than the West African clade [30–32]. Smallpox viruses can survive outside the body for long periods of time, making surfaces such as bed sheets and doorknobs a potential vector for transmission [33].

Zoonotic transmission occurs through direct contact with blood and body fluids and inoculation via mucocutaneous lesions of an infected animal, as well as through direct contact with or consumption of one of the natural viral hosts. Nosocomial transmission has also been reported [34–37].

The sex distribution of cases in the current outbreak shows a strong bias, with more than 95% of cases found in young men (<40 years). Spread among men who have sex with men (MSM) has been noted [38, 39], but heterosexual intercourse should also be considered. Such MPV spread among MSM groups could be accidentally introduced into the community. As previously reported, sexual transmission has been suspected among infected individuals with groin and genital lesions [40]. Rimoin et al. reported a 20-fold increase in the number of cases in the Democratic Republic of Congo between the 1980s and mid-2000s [41].

Monkeypox: is the basic reproduction number (R0) changing?

The reproductive number R0 for the Central African clone is estimated to be between 0.6 and 1.0 [41]. The R0 has not been estimated for the West African clade of MPVs, but it is assumed to be lower than that of the Central African clade. The upper limit R0 of 1.0 in the Central African clade suggests that the viruses not only maintain human-to-human transmission but can also persist in human

populations. If, as expected, the R0 value of the West Africa clade is much lower than that estimated for the Central Africa clade, then sustained human-to-human transmission and persistence in the human population are highly unlikely, and outbreaks will be largely due to spillover events from zoonotic hosts. This would make containment relatively easy, especially considering that almost all transmissions are likely to occur during the symptomatic period. The number of cases in the UK and evidence of ongoing transmission in people outside Africa, however, are the latest signs that the virus is changing its behavior. More research is needed to understand whether there is a genetic basis for the unprecedented spread of the virus. The genome of the monkeypox virus is enormous compared to that of many other viruses—more than six and sixty times larger than the genomes of the SARS-CoV-2 and hepatitis B virus, respectively. With few nucleotide sequences available in databases, many uncertainties remain.

As DNA viruses, poxviruses are usually slow to mutate but can still show rapid host adaptation through gene duplication and formation of “gene accordions” [42]. The evolutionary rate of the variola virus appears to be about 1×10^{-5} substitutions per site per year [43], which would correspond to about 1–2 nucleotide changes per year.

The incipient molecular characterization and genomic evolution analysis of the recently identified MPV isolates from Portugal, Belgium, Germany, and the USA suggest infections by the same specific lineage [44–47]. However, when MPV nucleotide sequences obtained from the USA and shared by CDC were included, the genomic epidemiology analysis and phylogenetic relatedness (www.nextstrain.org/monkeypox; [48]) show that two distinguishable outbreaks appear to coexist. A comparison with UK isolates characterized during the 2017–2019 outbreak suggests that the strains initially shared more than 40 single nucleotide substitutions. As most of these substitutions are G-to-A, it is plausible that APOBEC3 single strand DNA deaminase editing activity may be involved [49]. As it appears that vaccinia virus replication is not affected by APOBEC3 family members [50], further genomic evolution analyses will be required.

Clinical characteristics

As cases increased in Africa in the 1970s, human monkeypox was thought to resemble smallpox in symptoms, severity, and mortality. However, unlike smallpox, monkeypox was associated with low human-to-human transmissibility. By 1980, fewer than 50 human cases of monkeypox had been reported and its clinical manifestations and epidemiology remained poorly characterized [51]. Most clinical data on monkeypox in humans comes from later observational outbreaks in Central and West Africa in the mid-1980s. After monkeypox infection, there is an incubation period of 10–21 days with fever, headache, body aches, and exhaustion. In addition to the smallpox-like prodromal stage, more than 90% of patients develop *severe lymphadenopathy* 1–2 days before the onset of the rash, which is a key distinguishing feature of human monkeypox that is absent in smallpox. It can be unilateral or bilateral and occurs in the submandibular, cervical, postauricular, axillary, or inguinal lymph nodes [52]. Typically, after 1 to 3 days, a rash with blisters and pustules resembling those of smallpox develops, eventually crusting over. An infectious period occurs during the first week of the rash [53]. The typical rash initially appears as maculopapular lesions, 2 to 5 mm in diameter, which become generalized after centrifugal spread. In some cases, a centripetal rash occurs, as in chickenpox. The skin lesions typically progress through papular, vesicular, pustular, and crusting phases over a period of 14–21 days before drying and leaving depigmented scars [54]. While the occurrence of perigenital, perianal, and perioral ulcers is frequent, there is no clear evidence that the virus can be transmitted through genital secretions and transmission through contact with pre-existing skin lesions without sexual activity has been documented, supporting the hypothesis that MPV can be transmitted after contact with non-sex-related lesions [40]. An oligosymptomatic clinical presentation with a low number of typical lesions could favor MPV spread. In recipients of the smallpox vaccine, monkeypox rash was milder and more pleomorphic, lymphadenopathy may be absent, and there were no deaths. However, the proportion of infected people who die from smallpox is unclear as data is scarce. Regarding monkeypox, most reported deaths have occurred in young children and immunocompromised individuals including people living

with HIV [24, 55–57], and infection during pregnancy can lead to miscarriage [58]. Chickenpox has become the greatest differential diagnostic challenge. In addition to smallpox and chickenpox, molluscum contagiosum, dermatitis herpetiformis, eczema herpeticum, rickettsialpox, and drug eruptions should be considered in the differential diagnosis of a vesiculopapular rash [59]. Recently, a retrospective observational study reported clinical features and longitudinal virological findings and response to off-label antiviral agents in seven monkeypox patients diagnosed between 2018 and 2021 in the UK [60]. This demonstrated differential viremia kinetics and prolonged detection of viral DNA in upper airway swabs, explaining the prolonged PCR positivity. Such virus excretion after resolution of the skin lesion is in several cases an argument for isolation for more than 3 weeks of isolation in several cases.

Laboratory testing

If monkeypox is suspected, this finding should be reported to the local health authorities immediately. Laboratory confirmation is required for a definitive diagnosis. Healthcare workers should collect an appropriate sample and have it transported safely to a laboratory of adequate capabilities. Suitable specimens for diagnostic testing include skin lesions—the roof or fluid from vesicles and pustules, as well as dry crusts and blood. The State Health Office may request additional samples. If possible, a biopsy is an option. At least two crusts or material from vesicles should be collected in separate sterile containers using a sterile scalpel or 26-gauge needle. The base of the vesicle should be blotted vigorously with a sterile cotton or polyester swab and the material placed on a clean slide and air-dried. Swab material should not be stored in transport media as dilution may affect future test results. The material should be stored on dry ice or at $-20\text{ }^{\circ}\text{C}$ for transport to the reference laboratory for diagnostic testing. Specimens that may contain monkeypox should be handled according to Biosafety Level 2 (BSL2) practices and with appropriate equipment and facilities. Therefore, samples should be packaged and shipped according to national and international requirements. Detection of viral DNA by PCR with sequencing is the preferred laboratory test due to its accuracy and sensitivity.

Lesion samples must be stored in a dry, sterile tube (not a virus transport medium) and refrigerated. Because of the short duration of viremia in relation to the time at which the sample is collected after the onset of symptoms, PCR blood tests are usually inconclusive and should not be routinely performed on patients. Histopathological analysis of material from monkeypox lesions is indistinguishable from that of smallpox. Histopathology shows necrosis of the stratum basal, the adjacent dermal papillae, and the stratum spinosum. Structures such as Guarnieri corpuscles can be seen in the cytoplasm of the epidermal cells. Electron microscopy of monkeypox lesions has shown abundantly large, brick-shaped *Orthopoxvirus* particles in the cytoplasm of infected epidermal cells. However, this method cannot distinguish *Orthopoxvirus* species [61]. Although isolation of poxviruses from blood is possible, particularly during the prodromal phase of viremia, data on the use of blood cultures to isolate MPV are lacking. As previously mentioned, *Orthopoxviruses* are serologically cross-reactive and antigen and antibody detection methods do not provide monkeypox-specific confirmation. Therefore, serology and antigen detection methods are not recommended for diagnosis or case investigation when resources are limited. In addition, recent vaccination with a vaccinia-based vaccine (e.g., in people who were vaccinated before smallpox was eradicated or in people who were recently vaccinated for a higher risk, such as *Orthopoxvirus* laboratory personnel) can lead to false-positive results. It is important for the interpretation of the test results that the samples are accompanied by patient information including (I) date of onset of fever, (II) date of onset, (III) date of sample collection, (IV) status of the individual (stage of the outbreak), and (V) age [62].

Prophylaxis and treatment

Smallpox vaccine

Perhaps the most important factor behind the current resurgence in monkeypox is that population immunization coverage against smallpox is declining worldwide. Smallpox vaccination reduces the chance of contracting monkeypox by about 85%. After four decades of the cessation of smallpox vaccination, the monkeypox virus appears to have an opportunity to

occupy the ecological and immunological niche once occupied by the smallpox virus. Two vaccines are available in Europe and North America that protect against smallpox and monkeypox. A live attenuated vaccine contained a smallpox virus called vaccinia that was grown in laboratories. *Vaccinus* is a Latin word relating to cows. The term “vaccinia” was introduced by Edward Jenner, and this agent was used for vaccination against smallpox. It is currently known as vaccinia virus that differs from the original cowpox virus early administered in Jenner’s vaccinations. Although the precise origin of such virus is unknown, it could be produced by genetic recombination after serial passage from cowpox or variola via [63]. The vaccinia virus, however, can replicate in recipients and sometimes cause serious side effects that kill one in every 1 million people vaccinated. The other vaccine is the only approved monkeypox vaccine that causes fewer side effects and uses a live, non-replicating form of vaccinia. It requires two doses 4 weeks apart. Animal studies indicate that the first dose works faster than the live attenuated vaccine, while the second dose increases the durability of protection. The US Food and Drug Administration (FDA) has approved this vaccine specifically for smallpox and monkeypox.

In 1968, researchers first reported that monkeys could be immunized against monkeypox by smallpox vaccination [64]. In a later analysis of 215 human cases of monkeypox (209 confirmed in the laboratory), Fine and colleagues calculated that prior smallpox vaccination, as defined by the presence of vaccination scars, conferred 85% protection against monkeypox [65]. Currently, CDC recommends pre-exposure smallpox vaccination for field investigators, veterinarians, animal controllers, and medical personnel who evaluate or care for patients with suspected monkeypox who have no contraindications to vaccination. The role of post-exposure vaccination is less clear. Based on evidence that post-exposure smallpox vaccination can be effective in preventing or ameliorating the disease, CDC currently recommends post-exposure smallpox vaccination for individuals vaccinated within 4 days of initial direct exposure to monkeypox and considering vaccination for individuals who were vaccinated within 2 weeks of the last exposure.

There are no data on the effectiveness of vaccinia immunoglobulin (VIG) in treating monkeypox

complications. The use of VIG can be considered in severe cases of monkeypox in humans, although it is not known if it is beneficial in this situation. VIG can be considered for prophylaxis in exposed individuals with severely compromised cellular immunity for whom smallpox vaccination is contraindicated.

Antiviral therapy

There are also medications to treat severe cases of monkeypox. One of these, tecovirimat, became the first drug approved by the FDA to treat smallpox in 2018 after showing it was safe in human studies and effective in animals with closely related viruses. Based on similar data, the FDA approved a second smallpox drug, brincidofovir, in 2021. A recent report shows that there was no clinical benefit, only serious toxicities, in three patients treated with brincidofovir in the UK in the past 3 years. In contrast, tecovirimat leads to a reduction in viremia and faster recovery without side effects [52].

Closing remarks

The COVID-19 pandemic is ongoing, and a third of Americans live in areas where transmission is high enough that mandates for wearing masks indoors are being reconsidered and reenacted. The H5N1 avian flu virus has afflicted domestic poultry populations in the USA, resulting in nearly 38 million birds being killed to stem the spread of the virus. As of now, more than 900 suspected human cases of monkeypox have been detected in at least 29 countries, leading some to fear the outbreak could herald a second pandemic. MPV, however, is very different from SARS-CoV-2. We have known MPV for decades, and, more importantly, we already have vaccines and treatments that can be used to help contain the current outbreak. Unlike our recent experience with SARS-CoV-2, this means we are not “starting from scratch.” Whether MPV created an enzootic reservoir outside of Africa remains to be seen. If this was the case, the public health implications are difficult to predict from the available data from Africa since there may be substantial differences in population densities, immunity, and levels of immunosuppression, particularly when the reservoir includes wild rodents in an urban setting.

Declarations

Conflict of interest The authors declare no competing interests.

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