Review Article **GMSMJ** **Greater Mekong Subregion Medical Journal**

Monkeypox: Prevalence, Diagnostics, and Prevention

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Received 18 April 2022 • Revised 28 April 2022 • Accepted 12 July 2022 • Published online 1 September 2022

Abstract:

Human monkeypox is a viral zoonotic disease that occurs mostly in the rain forests of central and western Africa. However, the disease recently emerged in the United Kingdom resident who had recently traveled to Nigeria. There are now more than 4100 confirmed infections in nearly 46 countries where outbreaks do not usually occur. Monkeypox virus is a double-stranded DNA virus that found to infect tissues ranging from the heart and brain to the ovaries and lymphoid tissue. It has a clinical presentation very similar to that of ordinary forms of smallpox, including flulike symptoms, fever, malaise, back pain, headache, and characteristic rash. Given this clinical spectrum, differential diagnosis to rule out smallpox is very important. There are no definitive therapies for human monkeypox; however, the smallpox vaccine can protect against the disease. Effective prevention relies on isolation of infected patients or animals, contact tracing, limiting the respiratory exposure to infected patients and ring vaccination with smallpox vaccine.

Keywords: Monkeypox virus, Tecovirimat, JYNNEOOS vaccine

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GMSMJ 2022; 2 (3): 185-196

Introduction

Monkeypox outbreaks that have started to reappear in the last month caused by the monkeypox virus (MPXV), a member of the genus *Orthopoxvirus* (family Poxviridae, subfamily Chordopoxvirinae).[1] Human monkeypox is a zoonotic disease, similar to variola virus (which causes smallpox), vaccinia virus (the virus used in the smallpox vaccine), cowpox virus, ectromelia, and camelpox.[1-5] Human monkeypox is clinically almost identical to ordinary smallpox, and therefore, since the global eradication of smallpox in 1977, much attention has been paid to monkeypox as a smallpox-like disease.[2,3] Additional attention was brought to Monkeypox recently when, in May 2022, it reemerged in western countries, causing a cluster.[2] According to the World Health Organization (WHO) nearly 4100 cases have been identified outside the virus's usual areas of circulation.[4,5] However, only a handful of articles in the medical literature have described the continuing occurrence of human monkeypox. Therefore, here we will review the current state of knowledge about human monkeypox, emphasizing epidemiologic characteristics, clinical features, diagnosis, treatment, and prevention.

Epidemiologic Characteristics

Monkeypox has presumably occurred in sub-Saharan Africa for thousands of years, ever since humans acquired the virus through direct contact with infected animals.[1-5] The reservoir for MPXV is still unknown, although there is data to suggest that monkeys are, like humans, incidental hosts and that the reservoir is likely to be one or more species of rodents or squirrels of secondary forest in central Africa.[1,6] Monkeypox was not recognized as a distinct disease until 1970, when the elimination of smallpox from Democratic Republic of the Congo (DRC) revealed the continued occurrence of a smallpox-like illness in rural area.[1]

Initial epidemiologic studies conducted from 1970-1979 detected a total of 47 cases of human monkeypox near sub-Saharan African rainforests, of which 38 occurred in the DRC and the remainder in Cameroon, the Central African Republic, Gabon, Cote d' Ivoire, Liberia, Nigeria, and Sierra Leone.[1,7] All cases in the DRC occurred in areas bordering tropical rainforests and appeared to be associated with animal contact. Seven were fatal and secondary transmission was determined to be the most likely cause of infection in 4 cases, with secondary attack rates of 7.5% among household family members and 3.3% among all susceptible contacts.[8]

WHO conducted an active surveillance program in the DRC, where 338 of the 404 recognized African cases occurred from 1970-1986.[8,9] An animal source of infection was suspected in 245 of the 338 cases, and secondary transmission from a human source was presumed in the remaining 93 cases. The majority of cases occurred in children, with a mean age of 4.4 years. These increases in secondary transmission rate (3 times the 9% rate for cases in the 1970s) and the age distribution were thought to reflect waning immunity since the discontinuation of vaccination. The longest documented chain of infection consisted of only 4 generations of person-to-person transmission, indicating that MPXV had little potential for epidemic spread.[10] Serological surveys from this period involving vaccine-naive children found that 12%–15% of participating children had antibodies against MPVX, but most did not have a history of compatible illness, suggesting that subclinical infection also occurred.[8,10-12]

From 1986-1992, only 13 cases were reported and none were reported from 1993-1995.[3,6,10-12] However, in 1996-1997, more than 500 suspected cases of monkeypox were reported in Kasai-Oriental province, DRC.[13] The percentage of secondary cases was much higher (78%) and the fatality rate much lower (1%–5%). Between 1 January

1998 and 31 December 2002, a total of 1265 suspected cases were reported to the DRC Ministry of Health, with 88 were due to MPXV based on PCR and culture.[1] Of the laboratory-confirmed cases, patient age ranged from 10 months to 38 years, with a mean age of 16.5 years and a median of 15.5 years. 26% of patients were <10 years of age, and 73.2% were <25 years of age.

In 2003, United State reported the first occurrence of MPXV disease cluster in outside Africa. Of 72 reported cases, 37 human cases were laboratory confirmed during an outbreak.[1] Native prairie dogs (*Cynomys* sp.) housed with rodents imported from Ghana in western Africa to US were thought to be the primary source of outbreak, as most of the infected people became sick after contact with pet prairie dogs.[1,14-16] Although viral transmission appeared to be by direct contact with an infected prairie dog, two of the patients provided direct care to their infected children.[14] Unlike African patients, most patients from the US outbreak had a mild, self-limited febrile rash illness; 18 were hospitalized, although some were hospitalized for isolation precautions only and there were no deaths associated with the outbreak.[17,18] Two child patients had serious clinical illness. The first developed severe encephalitis a very rare complication of monkeypox and required intensive care unit hospitalization.[14,17,18] The second child was hospitalized with profound painful cervical, tonsillar lymphadenopathy and diffuse pox lesions, including lesions throughout the oropharynx.[14,17,18] Interestingly, only one child patient had a generalized rash similar to that seen in previous African patients, whereas many patients developed only localized lesions on the hands and fingers associated with direct contact with infected animals.[14,17,18] In 2018 and 2019 United Kingdom (UK) and Singapore reported first cases of monkeypox infections and later 2021 UK alone reported three additional domestic cases.[19,20]

Currently, there is an ongoing monkeypox outbreak of west African clade MPXV in predominantly Europe, with cases also in the Americas, Asia, Africa, and Australia.[2,4,5] The outbreak was initially reported in May 2022 in a United Kingdom resident who had recently traveled to Nigeria.[2,4,5] As of April 2022, 33 countries have confirmed cases, totaling to 1489 cases with 45 suspected in over 10 other countries.[4,5] The 2022 outbreak is exhibiting a different transmission pattern compared to other outbreaks outside of Africa with an increased frequency of human to human transmission, particularly in prolonged close contact.[2,4,5,21,22] Most of the cases observed so far have been in men, with a significant number being among active homosexual men, suggesting that sexual activity is a likely method of transmission.[2,4,5,21,22] This is possibly due to having close contact with infectious skin lesions during sexual relations.[2,4,5,21,22] It should be noted however, that monkeypox is not considered to be a sexually transmitted disease. The US Centers for Disease Control and Prevention (CDC) reported genomic data showing that there are at least two strains of the monkeypox virus responsible for the outbreaks.[5] This finding suggests that the virus might have been circulating internationally for longer than was thought. No deaths from monkeypox have been reported outside Africa so far this year; however, 4.7% of people who have contracted monkeypox across seven countries in West and Central Africa in 2022 have died.[2,4,5,21,22]

Diagnosis

As the clinical picture of monkeypox is very similar to that of chickenpox and smallpox, definitive diagnosis is key to keeping natural disease under control or in the early detection of outbreaks.[14] The differential clinical diagnosis for patients with monkeypox, chickenpox, or smallpox

are shown in table 1.[1] Although clinical characteristics can be useful in distinguishing poxvirus infections from other causes of vesiculopustular rashes, laboratory confirmation is required for a definitive diagnosis. During active infection, laboratory confirmation can be performed by various diagnostic assays including virus isolation and electron microscopy, PCR, IgM and IgG ELISA, immunofluorescent antibody assay, and histopathologic analysis.[1,14,22-26] However, histologically, the lesions of monkeypox are similar to other viral exanthems due to variola, cowpox, varicella-zoster, and herpes simplex viruses and include ballooning degeneration of keratinocytes, prominent spongiosis, dermal edema, and acute inflammation.[1] However, immunohistochemistry analysis, including use of either polyclonal or monoclonal antibodies against all orthopoxviruses, can differentiate between a herpes virus and poxvirus infection.[1,2,14,15,21-23,25-27]

Characteristic poxvirus virions showing the typical brick shape with lateral bodies and a central core would be expected to be observed under electron microscopy (Figure1).[4] Virus isolation, growing in mammalian cell culture (propagated in Vero E6 cells or BS-C-1) and characterization by various PCR techniques, followed by restriction fragment length polymorphism analysis or whole genome sequencing are considered to be definitive for the identification of MPXV.[1,2,14,15,21-23,25-27] Additionally, the availability of various real-time PCR assays that use panorthopoxvirus or MPXV-specific targets and DNA oligonucleotide microarray with the TNF receptor gene *crmB* has also been developed as another rapid method for species-specific detection of orthopoxviruses.[1,2,14,15,21-23,25-27]. Given the ease of transmission through direct contact and aerosol particles, specimens such as scab or other cutaneous tissues should be handled with care and collected aseptically with respiratory precautions.

The clinical features of human monkeypox closely resemble those of ordinary smallpox.[1-7,13,21,22,28] It was first reported as a human disease in a 9-month-old Zairean child in 1970.[7,8,29] It is believed that the virus is transmitted to humans during handling of infected animals or by direct contact with the infected animal's body fluids or lesions.[7,8,29,30] Person-to-person spread by large respiratory droplets during prolonged face-to-face contact can occur but is much less efficient than that seen with smallpox.[1-7,13,21,22,28] After a 10-14 day incubation period, prodromal illness with fever, malaise, and swollen lymph nodes is observed in most patients before rash development.[1-7,13,21,22,28] Other signs and symptoms of monkeypox include chills and/or sweats, headache, backache, sore throat, cough, and shortness of breath. Lymphadenopathy, which has been observed in 90% of unvaccinated patients, is not a common feature of smallpox and is therefore considered to be a key distinguishing feature of monkeypox (Figure 2 and 3).[1-7,13,21,22,28] Lymph node enlargement can occur in the submandibular and the cervical or inguinal regions. The prodromal period generally lasts 1–3 days before the occurrence of the typical maculopapular rash.[1-7,13,21,22,28] During the first week of the rash, the patient is considered to be infectious and should be isolated until all scabs separate and throat swab PCR results are negative.[1-7,13,21,22,28] The mean diameter of the skin lesions is 0.5–1 cm, and the clinical progress is very similar to that of ordinary smallpox lesions.[1-7,13,21,22,28] During a 2–4-week period, lesions progress from macules to papules, vesicles, and pustules, followed by umbilication, scabbing, and desquamation (Figure 2).[1-7,13,21,22,28] The rash starts mainly on the trunk, but can spread in a peripheral distribution to the palms and soles of the feet. Lesions can be observed on mucous membranes, in the mouth and tongue, and on genitalia.[1-7,13,21,22,28]

In addition to skin lesions, extracutaneous manifestations, such as secondary skin and/or soft-tissue infection (19% of cases), pneumonitis (12%), ocular complications (4%–5%), and encephalitis (<1%) can be observed in patients infected with MPXV.[1-7,13,21,22,28] The fatality rate is 10%, and death generally occurs during the second week of the disease.[1-7,13,21,22,28]

Table 1 Differential clinical diagnosis of patients with monkeypox, smallpox, and chickenpox.

Characteristics	Monkeypox	Chickenpox	Smallpox
Recent contact with exotic animal	Yes	No	No
Recent exposure to a patient with vesicular rash	Yes	Yes	Yes
Time period			
Incubation period, days	7–17	7–17	12–14
Prodrome period, days	1–4	2–4	0–2
Rash period (from the appearance of lesions to desquamation), days	14–28	14–28	10–21
Symptom			
Fever, severity	Moderate	Severe	Mild or none
Malaise, severity	Moderate	Moderate	Mild
Headache, severity	Moderate	Severe	Mild
Lymphadenopathy, severity	Moderate	None	None
Lesions			
Depth (diameter in mm)	Superficial to deep (4–6)	Deep (4–6)	Superficial (2–4)
Distribution	Centrifugal (mainly)	Centrifugal	Centripetal
Evaluation	Heterogeneous rash	Heterogeneous rash	Heterogeneous rash
Time to desquamation, days	14–21	14–21	6–14
Frequency of lesions on palms or soles of feet	Common	Common	Rare

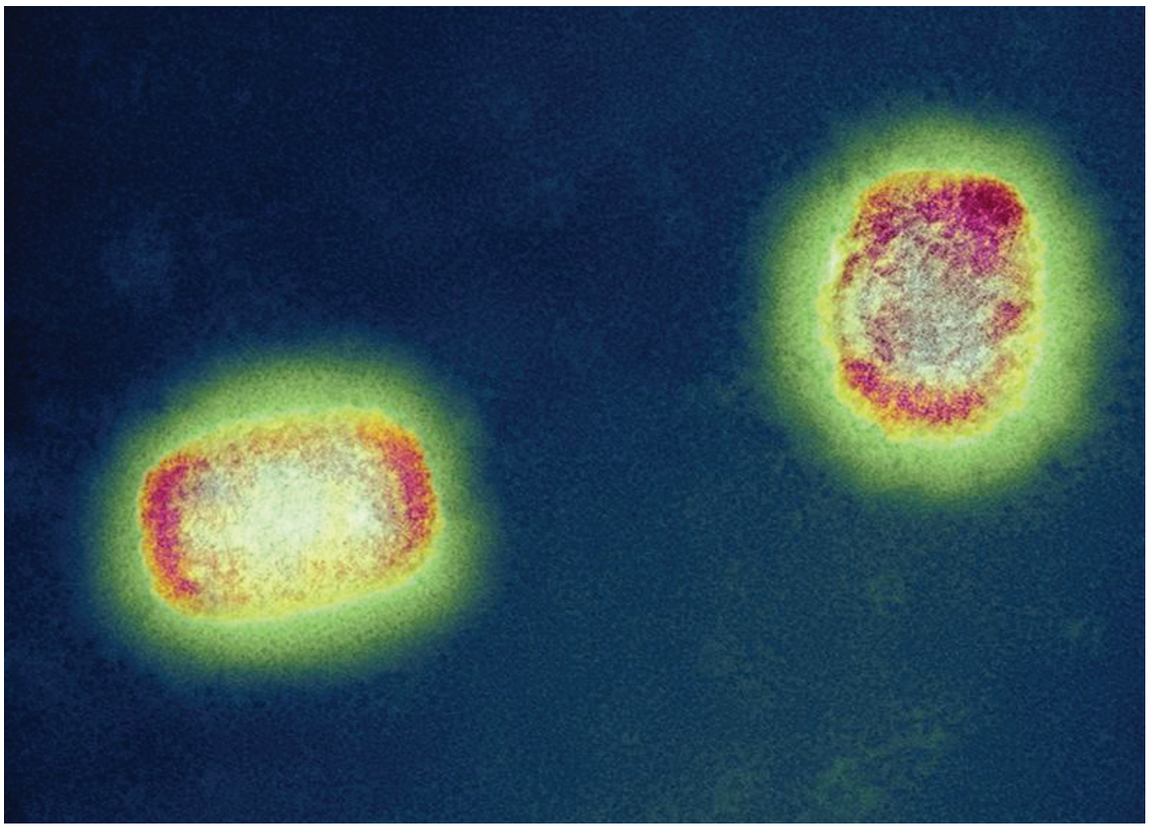

Figure 1 The monkeypox virus, a brick shape with lateral bodies and a central core shown here in a colored electron micrograph[4]

Figure 2 A, A 3-year-old African boy with monkeypox and axillary lymph node enlargement *(arrow)*. B, A 7-year-old African girl with monkeypox and bilateral inguinal lymphadenopathy *(arrows)*. For both patients, lymphadenopathy was the main differential diagnostic criterion that distinguished monkeypox from smallpox. C, A 7-year-old girl from Tokondo village, Kasai-Oriental province, Democratic Republic of Congo, with reported exposure to a dead monkey. Note the characteristic pustules on her back.[1]

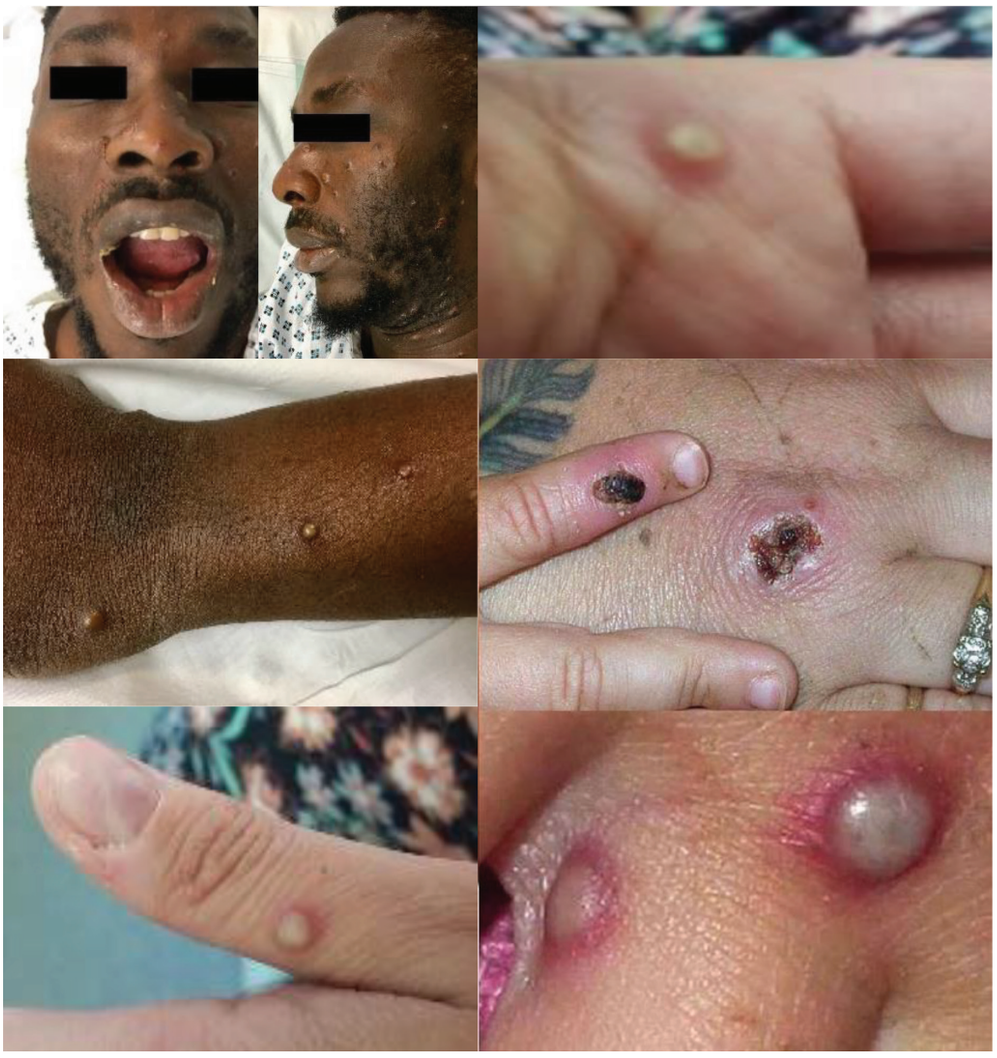

Figure 3 Skin and soft tissue manifestations of monkeypox; the early skin lesions are vesicles, which form into pustules that typically have an umbilicated centre. Their size can be variable.These skin lesions ulcerate and heal with crusting and scabbing.[19,20]

Genomic epidemiology of monkeypox virus

MPXV is a 197 kb linear DNA genome including 190 nonoverlapping ORFs > 180nt in length.[1,7,26,31] The central coding region sequence (CRS) at MPXV nucleotide locations 56000–120000 is highly conserved and flanked by variable ends that include inverted terminal repeats (ITRs), like with other orthopoxviruses (Figure 4).[31] The core region of the MPV genome encodes structural and essential enzymes and is like the variola virus by 96.3%. Despite this, the terminal regions of the MPV genome that encode virulence and host-range factors differ considerably. Comparing the genomes of MPV and smallpox virus demonstrates that MPV is a distinct species that evolved from an orthopoxvirus ancestor independently of variola virus.[31] The 2022 monkeypox virus is most closely related to viruses associated with the exportation of monkeypox virus from Nigeria to several countries in 2018 and 2019, including the UK, Israel, and Singapore.[31] The outbreak virus differs by a mean of 50 SNPs from the 2018–2019 viruses, which is far more than one would expect given the estimated substitution rate for Orthopoxvi-

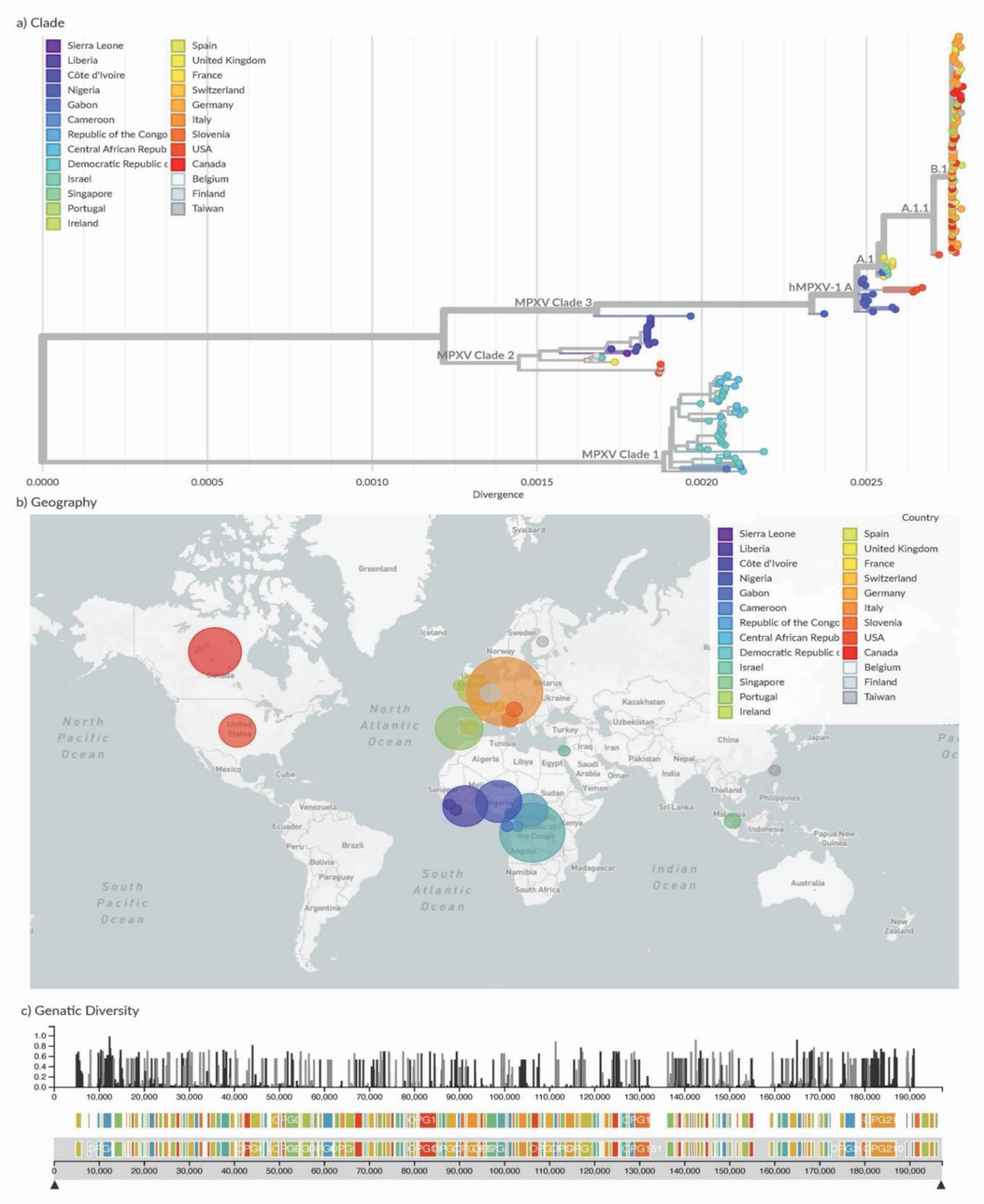

Figure 4 Genomic epidemiology of monkeypox virus, built with nextstrain/monkeypox[31], enabled by data from GenBank. a) Phylogenetic analysis of monkeypox clade, b) geographical distribution of different clades and c) genomic diversity.

ruses. Gene loss events have already been observed in the context of endemic Monkeypox circulation in Central Africa, and they have been linked to human-to-human transmission.[31] The microevolution scenario also implies that genome sequencing may provide sufficient resolution to track virus spread in the context of the current outbreak. There are two clades of monkeypox virus: West African and Congo Basin (Central African). Although infection with the West African monkeypox virus may cause significant sickness, the disease is typically self-limiting. The case-fatality ratio for the West African clade has been estimated to be less than 1%, but it may surpass 10% for the Congo Basin clade.

Prevention and Treatment

Unfortunately, eradication of monkeypox is not possible because of the existence of an animal reservoir.[1-7,13,21,22,28] However, vaccination with vaccinia virus (smallpox vaccine) is highly protective against infection with MPXV.[1-7,13,21,22,28,32] Researchers in the 1960s showed that monkeys could be successfully immunized against monkeypox by smallpox vaccination.[30] Additionally, not only were reduced numbers of human monkeypox cases observed in Africa among persons who were vaccinated, many of the cases were extremely mild (with very few lesions), and some cases may have been subclinical.[1] Because the virus that causes monkeypox and the virus that causes smallpox are so closely related, smallpox vaccination may also protect against monkeypox. According to African investigations, smallpox vaccination is at least 85% effective in preventing monkeypox. For these reasons, the Centers for Disease Control and Prevention recommends pre-exposure vaccination for research persons, health care workers, anyone who has direct contact with suspected MPXV-infected animals or infected persons, and laboratory workers who handle specimens that may contain MPXV.[2,4,5,21,22] JYNNEOS™ (also known as Imvamune or Imvanex) has been approved in the United States for the prevention of monkeypox and smallpox.[2,4,5,21,22] In terms of postexposure treatment, vaccination within 4 days after initial close contact with a confirmed monkeypox case is recommended by the Centers for Disease Control and Prevention; however, vaccination should be considered up to 14 days after exposure.[2,4,5,21,22] It is unknown whether a person with severe MPXV infection will benefit from treatment with immune globulin, and such therapy may be considered as a prophylactic for use in an exposed person with severe immunodeficiency in T cell function for whom smallpox vaccination would be contraindicated.[1,2,4,5,21,22]

There are currently no directly licensed antiviral drugs available for the treatment of MPXV infection.[21] In the 1950s, a number of thiosemicarbazone derivatives were found to inhibit the replication of vaccinia virus. Specifically, methisazone became the first antiviral drug to be introduced into clinical use, but it was fairly toxic when administered systemically and is no longer in use.[1] Cidofovir is a broad-spectrum antiviral drug that has activity against many DNA viruses, including MPXV, and treating cytomegalovirus retinitis in patients with AIDS.[1] Cidofovir has not been used to treat orthopoxvirus infection in humans but has been tested extensively in laboratory animals.[33] The antiviral therapy, tecovirimat (Tpoxx), is approved for smallpox by US FDA and is being studied for monkeypox treatment. Studies using a variety of animal species have shown that tecovirimat is effective in treating disease caused by orthopoxviruses.[19] Clinical trials in people showed the therapy was safe and had only minor side effects.[19] In addition, tecovirimat was given to one patient who had monkeypox.[19] The patient received 600 mg of the therapy twice a day for 2 weeks and experienced a shorter duration of illness and viral shedding.[19]

For the ongoing outbreak, countries are taking a variety of precautions to prevent transmission and contain the outbreak.[2,4,5,21,22] In the United States, post-exposure smallpox vaccination are being performed and alerts are going to the general populace and directed towards homosexual and bisexual men.[2,4,5,21,22] Similarly, the United kingdom has purchased smallpox vaccines and is investigating other related treatments and has issued health advisories as well.[2,4,5,21,22] Some countries, such as Thailand, are taking precautions such as airport screening or travelers from at-risk areas, planning purchase of smallpox vaccines, and screening local monkeys and imported livestock.

Conclusion

Monkeypox occurs mainly in the jungles of central and western Africa. The disease, unlike smallpox, is a typical zoonosis in that most cases occur as a result of direct contact with an infected animal. The symptoms of the disease in humans can be very similar to those of smallpox, chickenpox, or other causes of vesiculopustular rash. As global monkeypox cases continue to rise, smallpox vaccines are thought to be effective against monkeypox infection. Although the vaccines are considered safe and effective for use in people with smallpox infection, they have had limited testing against monkeypox. Therefore, accurate and rapid laboratory diagnostics, contact-tracing, and as well as the ability to quickly vaccinate any high-risk contacts are paramount in controlling an outbreak.

Acknowledgments

We thank the Centers for Disease Control and Prevention (CDC) and European Centre for Disease Prevention and Control (ECDC) for providing the necessary information.

Funding

Dhammika Leshan Wannigama was supported by Second Century Fund (C2F) Fellowship, Chulalongkorn University, Bangkok, Thailand, and the University of Western Australia (Overseas Research Experience Fellowship).

Potential conflicts of interest

All authors declared no conflicts of interest.

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