Human monkeypox infection

Authors: Anna Daunt[A] and Geraldine O'Hara[B]

ABSTRACT

Cases of monkeypox, a double-stranded DNA virus that is closely related to smallpox, have recently increased in non-endemic countries, prompting fears of a new health emergency. Tens of thousands of cases have now been reported globally, with the majority of locations not having historically reported monkeypox. Here we review the epidemiology, transmission, diagnosis, management and prevention of monkeypox.

Background and epidemiology

Monkeypox is an orthopox virus, a double-stranded DNA virus that is closely related to smallpox. It was first discovered in Copenhagen in 1958 after two outbreaks occurred in monkeys imported from Singapore for polio vaccine research.[1] Further outbreaks in non-human primates occurred in laboratories in the USA in 1959 and 1960 and in a zoo in the Netherlands in 1964.[2,3] However, it was not until 1970 that the first human case was identified in a 9-month-old baby from the Democratic Republic of the Congo (DRC), who was diagnosed through a smallpox surveillance programme after presenting with fever and rash.[3] It is important to reflect upon the fact that our knowledge of monkeypox relates to eradication of smallpox; in order to declare smallpox eradication successful, pustular rashes in previously smallpox endemic areas were closely characterised by the World Health Organization (WHO) Smallpox Eradication Programme.[4]

There are two clades (a 'clade' in this context is a group of monkeypox viruses that share the same common ancestor) of monkeypox virus; the Central African / Congo Basin clade and the West African clade.[5] The majority of monkeypox cases occur in the DRC, which has reported >1,000 suspected or confirmed cases a year since 2005.[6] Prior to the last decade, less than 10 infections had been reported in West Africa. In 2017, a large outbreak in Nigeria began, with over 200 confirmed and 500 suspected cases.[7] Altogether, monkeypox infection has currently been reported in 11 African countries: Benin, Cameroon, the Central African Republic, DRC, Gabon, Cote d'Ivoire, Liberia, Nigeria, the Republic of the Congo, Sierra Leone and South Sudan.[6,8] There is likely significant under-ascertainment of cases, as testing requires access to molecular diagnostics, such as PCR, which is not widely available in all countries, coupled with the fact milder cases may not come to the attention of local health networks.

Authors: [A]infectious diseases registrar, Guy's and St Thomas' NHS Foundation Trust, London, UK; [B]infectious diseases consultant, Guy's and St Thomas' NHS Foundation Trust, London, UK

Imported cases to non-endemic countries outside of Africa occur sporadically. In 2003, an outbreak in the USA of 47 cases in Illinois, Indiana, Kansas, Missouri, Ohio and Wisconsin was traced back to contact with prairie dogs.[9] This was, in turn, traced back to a shipment of small mammals from Ghana, which were housed in close proximity to prairie dogs later housed as pets. No human-to-human transmission is thought to have occurred in this outbreak. Between 2018 and May 2022, there were five cases of imported infection to the UK, with onward transmission to a further three

Key points

Monkeypox is an orthopox virus, a double stranded DNA virus that is closely related to smallpox. There are two clades, the West African clade and the Central African clade, the latter is associated with higher morbidity, mortality and greater human-to-human transmission.

There is currently an ongoing outbreak of monkeypox in a large number of non-endemic countries that is mainly affecting gay, bisexual or other men who have sex with men. In contrast, prior to 2022, community transmission of monkeypox had not occurred outside of Africa, with most cases occurring in the Democratic Republic of the Congo.

Monkeypox presents with typical skin lesions that have a characteristic pattern of evolution; macules, to papules, to vesicles, to pustules then to scabs, but the extent and location of these lesions are highly variable. Systemic symptoms are also common.

Key complications include secondary bacterial infection, abscesses, proctitis, penile oedema, eye involvement, pneumonitis and encephalitis.

Treatment is mostly supportive and centres on management of symptoms and prevention or treatment of complications. Preventative measures such as isolation policies, infection control measures and, more recently, vaccination play key roles in containment of outbreaks.

KEYWORDS: monkeypox, zoonosis, community transmission, non-endemic countries, outbreak

DOI: 10.7861/clinmed.2022-cme-mpox

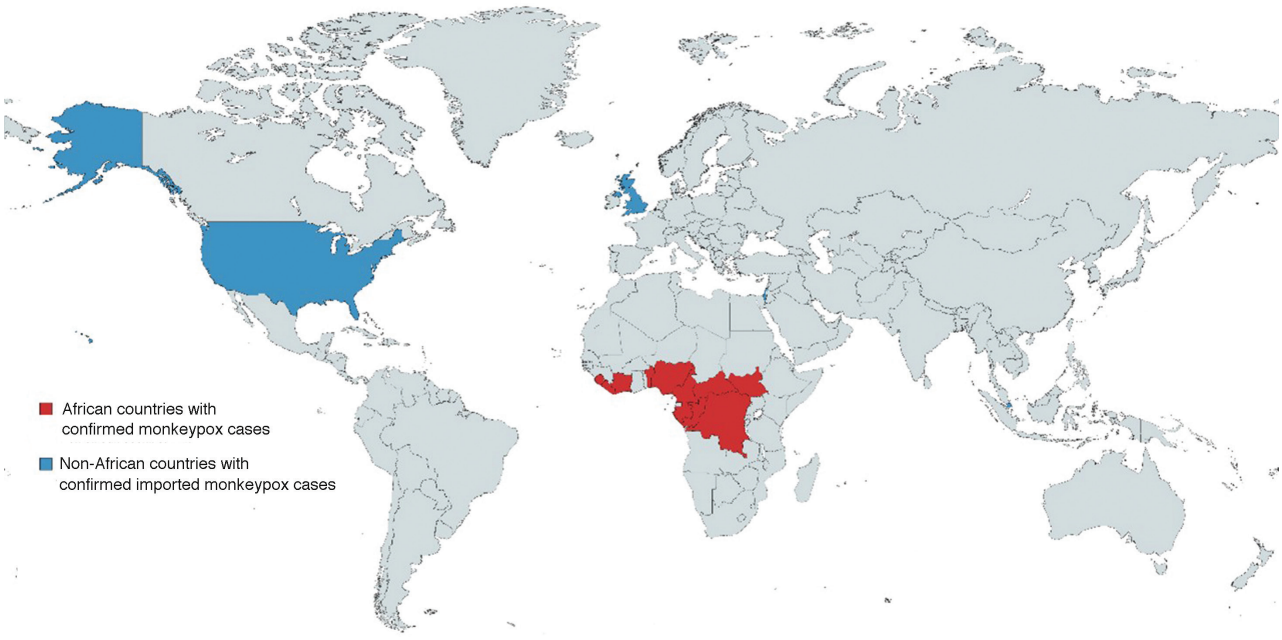

Fig 1. Distribution of confirmed human monkeypox cases prior to the 2022 global outbreak. Created using mapchart.net and reproduced with permission under Creative Commons Attribution-ShareAlike 4.0 International Licence.

individuals, as well as two infections in the USA, and single cases in Singapore and Israel.[10] Outside of these instances, there had been no other reports of monkeypox in non-endemic countries (Fig 1).

Endemic countries have experienced a recent increase in cases of monkeypox and this was rapidly identified as concerning by several researchers from these regions.[11] However, there remained a lack of support from the international community to help these countries tackle outbreaks or to advance research into epidemiology and transmission.[12] The majority of the affected countries have limited testing and surveillance capacities, and no endemic countries currently have access to vaccination. A notable contrast exists between the financial, scientific and political commitment to monkeypox in endemic versus non-endemic countries.

In May 2022, two individuals in the UK were diagnosed with monkeypox who had no recognisable epidemiological link to endemic countries.[13] Within the next week, 20 more cases were diagnosed in the UK, with further cases being reported in other high-income non-endemic countries.[13,14] As of 29 August 2022, there have been 3,279 confirmed cases of monkeypox in the UK, of which, 70% have occurred in London.[14] Worldwide, 53,027 cases have been confirmed in 100 countries, 93 of which have never historically reported cases of monkeypox.[15]

As well as the geographic difference between the current and previous outbreaks, there are also key demographic differences. Early outbreaks predominantly affected children, while more recent outbreaks in West and Central Africa have affected individuals of all ages.[16] It is thought this change in demographic population may relate to an increasing proportion of the population having no pre-existing immunity from smallpox vaccination, as well as waning immunity from vaccination in older adults.[17,18] While some reports of recent outbreaks in West and Central Africa have noted that a higher proportion of men are affected, the demographics of the current outbreak are striking, as over 99% of cases have occurred in men, and the overwhelming majority have occurred in gay, bisexual or other men who have sex with men (GBMSM).[11,19–25]

Transmission

Monkeypox is a zoonosis and has been found in several animal hosts; despite the disease's name, rodents appear to be the most important animal reservoir.[2] Transmission can occur from direct contact with the blood, bodily fluids or mucosal lesions of animals. The extent to which animal-to-human transmission has contributed to spread in previous outbreaks is variable; this was the cause of 100% of cases in the US outbreak of 2003, while outbreaks in DRC have varied from <22% to >94%.[17,18]

Human-to-human transmission is well described, and can occur through direct contact with infected material (eg skin lesions or contaminated bed linen) or via respiratory transmission. Overall, transmissibility was historically felt to be low. A systematic review of previous outbreaks reported a secondary attack rate of 0%–11% in unvaccinated household contacts.[19] Sleeping in the same room, living in the same household and sharing dishes have been identified as risk factors. In the 2022 outbreak, the confinement of cases to the GBMSM community, and the high burden of genital lesions has demonstrated likely transmission during sexual contact. Monkeypox DNA has also been found in semen of infected individuals; however, whether transmission has occurred through skin-to-skin or direct sexual transmission requires further investigation.[23]

Clinical features

Monkeypox causes distinctive skin lesions that have a characteristic pattern of progression: macules, then papules, then vesicles, then pustules that eventually scab over and resolve (Fig 2).[24] Lesions may progress at different rates and so different stages may co-exist simultaneously.[25,26] Widespread maculopapular rash, distinct from these discrete lesions, has also been reported.[25,26] The location and extent of lesions is variable. Single lesions have been seen in approximately 10% of cases, while some patients have hundreds of lesions.[23,26] Cutaneous

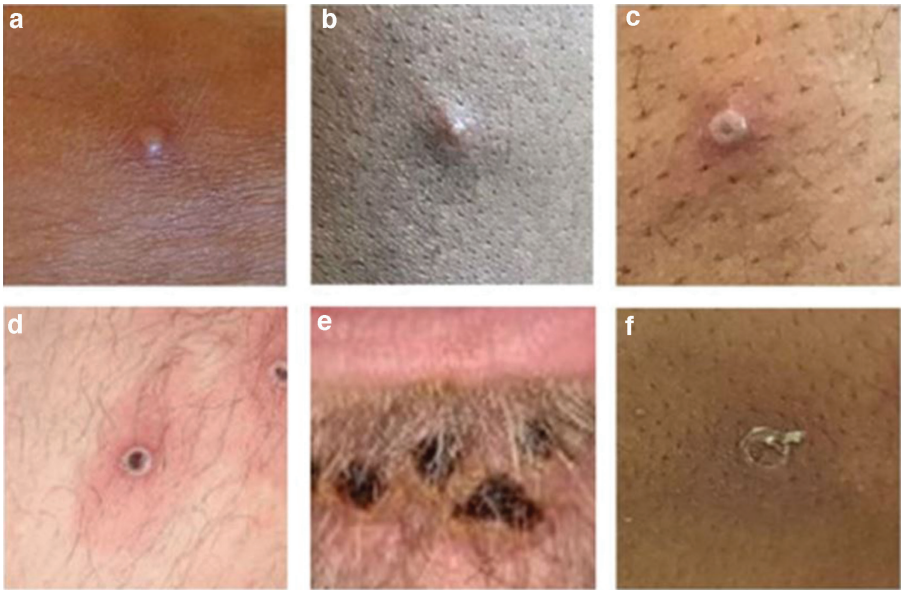

Fig 2. Characteristic progression of monkeypox lesions. a) Early vesicle, 3 mm diameter. b) Small pustule, 2 mm diameter. c) Umbilicated pustule, 3–4 mm diameter. d) Ulcerated lesion, 5 mm diameter. e) Crusting of mature lesions. f) Partially removed scab. Reproduced from UK Health Security Agency. *Guidance: Monkeypox: background information*. UK Health Security Agency, 2022. under the Open Government Licence v3.0.

lesions can occur anywhere on the body and mucosal lesions are also common. In previous outbreaks in endemic regions, lesions were most commonly seen on the face, limbs and body.[11,20–23,25,26] Later studies from Nigeria showed higher rates of genital lesions and, in the current 2022 outbreak, genital and perianal lesions have been present in the majority of patients.[11] Oropharyngeal lesions or symptoms are also now well described.

Systemic features are also common and can occur before or after the onset of skin lesions. Common symptoms are fever, lethargy, myalgia, arthralgia and headache. Lymphadenopathy is a key feature of monkeypox and is recognised as a key distinguishing clinical feature from smallpox. In the current outbreak, inguinal lymphadenopathy has been particularly prominent.[23,25,26] Asymptomatic cases have now been identified, but the frequency of these cases or their contribution to transmission is not yet known.[27]

The incubation period is approximately 12 days and symptoms usually last 2–4 weeks. Lesions are considered infectious until they have scabbed over, and the scab has fallen off with a new layer of skin underneath. The illness is generally self-limiting; however, there are a number of potentially serious complications. Severe pain, proctitis, penile swelling and abscesses may necessitate hospital admission, while secondary bacterial infection, pneumonitis, encephalitis and keratitis can be life or sight threatening.[22,23]

In the current outbreak, hospitalisation rates of approximately 10% have been reported, although this may fall as the outbreak progresses.[23,25,26]

In outbreaks in endemic regions, pooled case fatality was 3.6% for the West African clade and 10.6% for the Central African clade.[17] Mortality was higher in young children, pregnant women and immunocompromised individuals. In the 2022 outbreak, 15 deaths have now been reported.[15] It is unclear whether this lower mortality rate is due to virological or biological differences, or confounded by variations in healthcare resources.

Diagnosis, management and prevention

Monkeypox is diagnosed through detection of viral DNA.[27] A pan-orthopox PCR and a monkeypox-specific PCR are routinely performed. Samples should be taken from the surface of a lesion, or, in close contacts without lesions, a throat swab should be taken. Urine and blood (EDTA) may be tested in follow-up testing of confirmed cases. Serological testing for orthopox immunoglobulin (Ig) G and IgM has been performed during investigations of previous outbreaks but is not used routinely in clinical practice, and the complexity of poxviruses, which are capable of producing over 200 proteins, makes developing robust serological assays challenging.[10]

In the current outbreak, approximately one-third of patients have a concomitant sexually transmitted infection and so testing for this should take place at point of diagnosis, as well as investigation of potential complications as guided by clinical presentation.[23,25]

Treatment of monkeypox remains largely supportive and focuses on alleviation of symptoms and management of complications (Box 1). Brincidofovir and tecovirimat, both of which have

Box 1. Key considerations when managing a patient with monkeypox infection

- Ensure that you are following local infection control guidelines to make sure that the patient is appropriately isolated and that you are wearing the correct personal protective equipment
- Take a full social history to establish if the patient can self-isolate and whether they have had contact with high-risk individuals (children, pregnant women and immunocompromised individuals)
- Offer support with symptom control, eg oral and topical analgesia and avoidance of constipation in proctitis/proctalgia
- Assess the patient for key complications, which may require hospital admission
- Offer testing for concomitant sexually transmitted infections
- Ensure that the case has been reported to the appropriate public health body (in the UK, monkeypox is a notifiable disease and should be reported to the local health protection team)

Table 1. Monkeypox factsheet

Type of virus	**Orthopoxvirus: double-stranded DNA virus**
Epidemiology	Prior to 2022: > confirmed cases in 11 countries, the majority of which occurred in the Democratic Republic of the Congo. Other countries include Benin, Cameroon, Central African Republic, Gabon, Cote d'Ivoire, Liberia, Nigeria, the Republic of the Congo, Sierra Leone and South Sudan > imported confirmed cases in USA, UK, Singapore and Israel. 2022 outbreak: > confirmed cases in 100 countries across the globe with further cases in other countries likely to occur. > vast majority of cases occurring in GBMSM.
Transmission	> Direct contact with infected material (eg lesions or bed linen). > Respiratory transmission. > Transmission during sexual contact (precise mechanism remains unclear). > Animal to human spread: direct contact with blood, bodily fluids or lesions.
Skin manifestations	> Typical lesions: from macules, then papules, then vesicles and then pustules that eventually scab over and resolve. > Number of lesions may vary from single lesions to hundreds of lesions. > Can occur anywhere on body (genital and perianal lesions common in 2022 outbreak). > Oropharyngeal and other mucosal lesions are now well described.
Systemic symptoms	> Fever, lethargy, myalgia, arthralgia, headache, sore throat and lymphadenopathy
Complications	> Severe pain, proctitis, penile swelling, abscesses, airway compromise, secondary bacterial infection, pneumonitis, encephalitis and keratitis.
Mortality rate	> West African clade (previous outbreaks) = 3.6%. > Central African clade = 10.6%. > 2022 outbreak <0.01%.
Treatment	> Treatment largely supportive: management of symptoms and complications. > Brincidofovir and tecovirimat have both been used previously and in the current outbreak.
Prevention	> Self-isolation for patients at home. > Strict infection control measures within healthcare institutions. > Third generation smallpox vaccine as pre-exposure prophylaxis to at-risk individuals and post-exposure prophylaxis to those with significant exposure history.

GBMSM = gay, bisexual or other men who have sex with men.

been approved in the USA for smallpox, have both been used through expanded access or compassionate use in patients with monkeypox, including in the current outbreak.[10,22,23] However, a lack of randomised controlled trials means that evidence confirming their efficacy is currently lacking, and a severely limited supply is a further barrier to widespread use.

Prevention of infection and cessation of ongoing community spread are the cornerstones to controlling outbreaks. Self-isolation policies for individuals with monkeypox can be effective but to be truly effective, they need underpinning with financial and social support. Within healthcare settings, strict infection control procedures limit spread. Pre- and post-exposure vaccination, using third-generation smallpox vaccines, are effective in preventing or reducing the severity of monkeypox infection. Vaccination has been used for some time in laboratory staff, and given to contacts of cases in Western countries that have had imported cases. In the current outbreak, it is now being distributed more widely, including to at-risk individuals in the GBMSM community as well as contacts. There are significant challenges associated with producing these vaccines at speed, as they are passaged in cell lines (Table 1).

As physicians and human beings, we must reflect on the abject lack of testing, treatment and vaccination for monkeypox in African countries. Infectious diseases do not respect international borders and investment in global health must prioritise equitable access unless we wish to face further outbreaks. ■

References

1 Von Magnus P, Andersen EK, Petersen KB, Birch-Andersen A. A pox-like disease in cynomolgus monkeys. *Acta Path Micro Scand* 1959;46:156–76.
2 Parker S, Bueller RM. A review of experimental and natural infections of animals with monkeypox virus between 1958 and 2012. *Future Virol* 2013;8:129–57.
3 Ladnyj ID, Ziegler P, Kima E. A human infection caused by monkeypox virus in Basankusu Territory, Democratic Republic of the Congo. *Bull World Health Organ* 1972;46:593–7.
4 Fenner F, Henderson DA, Arita I, JeZek Z, Ladnyi ID. *Smallpox and its eradication*. World Health Organization, 1988.
5 Likos AM, Sammons SA, Olson VA *et al*. A tale of two clades: monkeypox viruses. *J Gen Virol* 2005;86:2661–72.
6 Durski KN, McCollum AM, Nakazawa Y *et al*. Emergence of monkeypox – West and Central Africa, 1970–2017. *MMWR Morb Mortal Wkly Rep* 2018;67:306–10.
7 Yinka-Ogunleye A, Aruna O, Ogoina D *et al*. Reemergence of human monkeypox in Nigeria, 2017. *Emerg Infect Dis* 2018;24:1149–51.

8 World Health Organization. *Monkeypox fact sheet*. WHO, 2022. www.who.int/news-room/fact-sheets/detail/monkeypox [Accessed 8 August 2022].
9 Centers for Disease Control and Prevention. *Monkeypox in the United States*. CDC, 2022. www.cdc.gov/poxvirus/monkeypox/outbreak/us-outbreaks.html [Accessed 8 August 2022].
10 Adler H, Gould S, Hine P *et al*. Clinical features and management of human monkeypox: a retrospective observational study in the UK. *Lancet Infect Dis* 2022;1153–62.
11 Ogoina D, Iroezindu M, James HI *et al*. Clinical course and outcome of human monkeypox in Nigeria. *Clin Infect Dis* 2020;71:e210–e214.
12 Kozlov M. Monkeypox in Africa: the science the world ignored. *Nature* 2022;607:17–18.
13 UK Health Security Agency. *Monkeypox cases confirmed in England – latest updates*. UK Health Security Agency, 2022. www.gov.uk/government/news/monkeypox-cases-confirmed-in-england-latest-updates [Accessed 8 August 2022].
14 UK Health Security Agency. *Monkeypox outbreak: epidemiological overview, 30 August 2022*. UK Health Security Agency, 2022. www.gov.uk/government/publications/monkeypox-outbreak-epidemiological-overview/monkeypox-outbreak-epidemiological-overview-30-august-2022 [Accessed 4 September 2022].
15 Centers for Disease Control and Prevention. *2022 Monkeypox Outbreak Global MAP*. CDC, 2022. www.cdc.gov/poxvirus/monkeypox/response/2022/world-map.html [Accessed 4 September 2022].
16 Breman JG, Kalisa-Ruti Steniowski MV *et al*. Human monkeypox, 1970–79. *Bull World Health Organ* 1980;58:165–82.
17 Bunge EM, Hoet B, Chen L *et al*. The changing epidemiology of human monkeypox-A potential threat? A systematic review. *PLoS Negl Trop Dis* 2022;16:e0010141.
18 Beer EM, Rao VB. A systematic review of the epidemiology of human monkeypox outbreaks and implications for outbreak strategy. *PLoS Negl Trop Dis* 2019;13e0007791.
19 Pittman PR, Martin JW, Kingebeni PM *et al*. Clinical characterization of human monkeypox infections in the Democratic Republic of the Congo. *medRxiv* 2022;2022.05.26.22273379.
20 Jezek Z, Szczeniowski M, Paluku KM, Mutombo M. Human monkeypox: clinical features of 282 patients. *J Infect Dis* 1987;156:293–8.
21 Ogoina D, Izibewule JH, Ogunleye A *et al*. The 2017 human monkeypox outbreak in Nigeria-Report of outbreak experience and response in the Niger Delta University Teaching Hospital, Bayelsa State, Nigeria. *PLoS One* 2019;14:e0214229.
22 Yinka-Ogunleye A, Aruna O, Dalhat M *et al*. Outbreak of human monkeypox in Nigeria in 2017–18: a clinical and epidemiological report. *Lancet Infect Dis* 2019;19:872–9.
23 Thornhill JP, Barkati S, Walmsley S *et al*. Monkeypox virus infection in humans across 16 countries – April–June 2022. *N Engl J Med* 2022;387:679–91.
24 UK Health Security Agency. *Guidance: Monkeypox: background information*. UK Health Security Agency, 2022. www.gov.uk/guidance/monkeypox [Accessed 8 August 2022].
25 Patel A, Bilinsk B, Tam JCH *et al*. Clinical features and novel presentations of human monkeypox in a central London centre during the 2022 outbreak: descriptive case series. *BMJ* 2022;378:e072410.
26 Girometti N, Byrne R, Bracchi M *et al*. Demographic and clinical characteristics of confirmed human monkeypox virus cases in individuals attending a sexual health centre in London, UK: an observational analysis. *Lancet Infect Dis* 2022;22:1321–8.
27 De Baetselier I, Van Dijck C, Kenyon C *et al*. Asymptomatic monkeypox virus infections among male sexual health clinic attendees in Belgium. *medRxiv* 2022;2022.07.04.22277226.

Address for correspondence: Dr Anna Daunt, Guy's and St Thomas' NHS Foundation Trust, Westminster Bridge Road, London SE1 7EH, UK.
Email: anna.daunt@gstt.nhs.uk