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Commentary

Monkeypox: An old foe, with new challenges

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SUMMARY

At first glance, a multi-country outbreak of monkeypox in 2022 seems unusual. However, the re-emergence and expansion of this viral disease beyond its endemicity in West and Central Africa had previously been predicted as a possible consequence of a decline in population immunity following smallpox eradication. Since the 13th of May 2022, cases of monkeypox have been reported in at least 28 WHO member states from within 4 regions (the Americans, European, Eastern Mediterranean and Western Pacific regions). This summary describes the multi-country outbreak to date, with an emphasis on patient demographics, common symptoms and signs, clinical management (including infection prevention measures) and clinical outcomes of the cases in the United Kingdom, which has so far reported the largest number of laboratory confirmed cases. The future implications of this outbreak, including preventative measures to curb the current outbreak, prevent future outbreaks and the likelihood of the disease becoming endemic in the UK are also discussed.

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Background

Monkeypox (MPX) is a DNA virus member of the *Orthopoxvirus* genus, Poxviridae family [1], historically responsible for disease in humans secondary to spillover from zoonotic hosts. The disease was named monkeypox following its discovery as the cause of severe poxviral disease in non-human primates under study in laboratories in Denmark in 1958. The first recorded human case occurred in 1970, reported in the Democratic Republic of the Congo (DRC) (formerly known as Zaire) and since then most cases have been reported across Central and West Africa. It was not until after 1980 and the eradication of smallpox, that MPX was studied with greater interest, particularly following increased funding to develop countermeasures for perceived biological threats, and with increasing emergence of cases as the legacy protection afforded by mass smallpox vaccination programs declined [1]. There are two known clades of MPX, West African (WA) and Congo Basin (CB), named for their geographic origin. The CB clade has been reported as the more virulent, with case fatality ratios (CFR) ranging from 1% to 10%, while the WA clade reported a lower mortality rate of $< 3\%$ [1–3]. Recently, the World Health Organization (WHO) has initiated a review into changing the

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name of the virus, its clades and the disease it causes following concerns over the potential discriminatory nature of the current nomenclature.

As a zoonotic virus, MPX is transmitted from infected reservoir animals to humans. It is believed that direct transmission may occur from bites, scratches, from exposure to lesions on infected animals, or exposure to their body fluids through hunting, skinning, trapping and cooking [3]. Despite its current name, the virus is not believed to have a stable reservoir in non-human primates. A variety of exotic rodent species have been suggested as possible reservoirs, including rope squirrels, tree squirrels, Gambian pouched rats, dormice and other species. Further evidence for this has been found during investigation into international cases of MPX in the past, though uncertainty remains over the exact reservoir and the mechanism of how the virus is maintained in nature [1].

The incubation period of MPX is typically 6—13 days but can be as long as twenty-one. A prodrome of clinical illness precedes lesion development and may last 1—5 days; symptoms during this period may include fever, headache, myalgia, lethargy and lymphadenopathy [2]. The latter is considered a distinctive feature of the disease, a study in the DRC described lymphadenopathy in 98.6% of the studied MPX cohort [4,5]. Typically, 1—3 days after subsidence of fever, a rash develops presenting sequentially as macules, papules, vesicles, pustules progressing to umbilication, before finally crusting over and resolving over a period of a few weeks. The sequential nature of the rash helps distinguish it from its closest differential, chickenpox, in which all four stages of the rash appear concomitantly. Diagnosis is best performed by PCR amplification of viral DNA from swabs of lesions or scabs, and to a lesser extent, from throat swabs, blood, urine and from skin [2,4,5].

Previous international outbreaks have varied significantly in their scale and routes of exposure. In 2003 a large outbreak in the USA consisting of 47 human cases was attributed to infection from contact with domesticated prairie dogs housed in close proximity to exotic rodent species which were confirmed to be infected with MPX [1,5]. In 2018, two unrelated cases were reported in the UK in travellers from Nigeria, with a subsequent nosocomial case in a healthcare worker epidemiologically linked to care of one of these cases. Further cases have been reported in the UK in 2019 and in 2020, and in USA in 2021, all linked to travellers returning from Nigeria and all infected with the WA clade [1]. Human to human spread was rare in these outbreaks and the incidents presented little to no threat to the wider population [1,2], following concerted public health efforts made to contain the outbreaks, with patients and contacts isolated for protracted periods. In the UK, High Consequence Infectious Disease (HCID) facilities were utilized in patient care [1,2].

The current MPX epidemic in 2022

Globally, as of 16th June, there have been 2103 laboratory confirmed cases in this outbreak, with 574 cases reported in the UK [6]. Amongst countries from which demographic data is so far available, 97% of the cases have occurred in men 0—65 years of age (median age 39 years) [7].

The current UK outbreak is considered as three "clusters"; a single traveller returning from Nigeria with no secondary cases, a family of two in London with no travel history and no onward transmission, and finally, a large outbreak, predominantly from those within the gay, bisexual and other men who have sex with men community (GBMSM) [6,8]. This group has been the most heavily impacted by the disease. Of 152 confirmed cases who participated in questionnaires, 151 identified as GBMSM [8]. In the UK there have been no deaths reported and few severe multi-system illnesses requiring high-level care. Vigilance for severity as well as transmission in other groups is important however, since groups prone to severe disease include those with HIV who have low CD4 counts, other immunocompromised states, children and pregnant women [9]. The probable and possible case definitions allow flexibility to identify these cases; more idiosyncratic cases may also be tested after discussion with local infection specialists [10]. While the early cases had samples from several sites tested, diagnosis is now usually based on PCR of a lesion swab [2,9].

Infection prevention and control guidance has reflected the evolving understanding of the transmission of the disease. Initially all confirmed cases of MPX in the UK were managed in HCID units. However, the majority of cases were well and could self-isolate at home. As the UK outbreak evolves and the clinical progression of disease becomes clearer, the designation of MPX as an HCID is likely to be under review.

Since transmission is primarily through close contact, assessment of suspect cases (in the absence of respiratory symptoms) has permitted the use of personal protective equipment (PPE) which protects from contact, droplet and fomite spread. This includes an apron, a fluid-resistant surgical mask and gloves. In the case of unwell patients or patients with respiratory symptoms, PPE use should include long-sleeved gown, FFP3 mask and eye protection since airborne transmission remains a potential route. Indeed, the alleged infection of a healthcare worker from changing a hospitalised patient's bedding, supports this level of PPE [11].

Although not designated a sexually transmitted disease, the potential for secretion of infectious virus in semen has not yet been ruled out [12]. Other DNA and RNA viruses have been shown to persist in semen long after clinical recovery [13]. As a precaution, pending further research, male patients with confirmed MPX are advised to use condoms for 8 weeks after complete recovery (including resolution of any lesions) [14].

Comparisons with the COVID-19 pandemic are expected and at this stage some of the challenges are familiar, ranging from stigma against certain societal groups to the need for scaled up (devolved) testing, financial support for those isolating at home and the production of rapid guidance in the face of ongoing clinical and epidemiological uncertainties.

There are significant differences. This outbreak, although worldwide, was first identified in the United Kingdom, with the first, unrelated cases providing a serendipitous link for astute clinicians. During this outbreak there are some causes for optimism; there has been recent experience of case management in UK hospitals [2]. Treatment [15] and vaccination [16] are already available and are being used, with the latter playing an important role in pre- and post-exposure prophylaxis. Smallpox vaccine confers approximately 85% protection against MPX [17]. Rapid sequencing of the virus has led to speculation that it may have been circulating in humans rather than animal reservoirs for some time and sharing of sequence data from multiple countries has facilitated this [18]. Furthermore, transmission predominating in specific subgroups allows for more targeted health promotion measures.

Table 1
Links to UK Government Guidance

Guideline	Link	Reference list
Monkeycpox cases confirmed in England — latest updates	https://www.gov.uk/government/news/monkeypox-cases-confirmed-in-england-latest-updates	[6]
Investigation into monkeypox outbreak in England: technical briefing 1	https://www.gov.uk/government/publications/monkeypox-outbreak-technical-briefings/investigation-into-monkeypox-outbreak-in-england-technical-briefing-1	[8]
Immunisation of individuals with underlying medical conditions	https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/857279/Greenbook_chapter_7_Immunsing_immunosupressed.pdf	[9]
Monkeypox: case definitions	https://www.gov.uk/guidance/monkeypox-case-definitions	[10]
De-isolation and discharge of monkeypox-infected patients: interim guidance	https://www.gov.uk/guidance/de-isolation-and-discharge-of-monkeypox-infected-patients-interim-guidance	[14]
Monkeypox vaccination guidelines	https://www.gov.uk/government/publications/monkeypox-vaccination	[16]
Qualitative assessment of the risk to the UK human population of monkeypox infection in a canine, feline, mustelid, lagomorph or rodent UK pet	https://www.gov.uk/government/publications/hairs-risk-assessment-monkeypox/qualitative-assessment-of-the-risk-to-the-uk-human-population-of-monkeypox-infection-in-a-canine-feline-mustelid-lagomorph-or-rodent-uk-pet	[20]

UK Government Guidance on monkeypox is updated constantly. Links provided in this table should update to most recent guidance.

Complexities more specific to this outbreak include the challenges in contact tracing, in particular among sexual contacts, and uncertainty about capturing non-GBMSM cases. The extensive overlap in acute rash presentation, in particular varicella zoster virus (VZV, chickenpox), enterovirus (hand, foot and mouth), herpes simplex viruses (HSV-1 and 2), secondary syphilis, lymphogranuloma venereum (LGV) and granuloma inguinale, has made clinical diagnosis more difficult.

Table 1 provides links to up-to-date UK government guidance.

Future implications

Presently, the precise global distribution of MPX is uncertain due to case ascertainment bias (encompassing a lack of diagnostic testing, clinical mis-classification and incomplete surveillance) in some countries. Although transmission chains have been relatively small in previous outbreaks, a decline in population immunity may lead to sustained epidemics with a basic reproduction rate (R_0) > 1 [19], as evidenced by this ongoing outbreak. For MPX to become endemic in the UK, pathogen sharing must occur with domesticated animals, in particular pet rodents, with transmission into wildlife species. Therefore, current advice from the UKHSA human animal infections and risk surveillance (HARIS) group is for temporary removal of these rodents from infected households for up to 21 days, and testing to exclude infection is recommended [20].

Within this current outbreak and in the future, MPX should be routinely considered in the spectrum of diseases when assessing patients presenting to genitourinary medicine clinics, as well as expanding multiplex PCR assays to include specific primers for pox viruses, both in the diagnostic laboratory or in rapid diagnostics to be utilized in the clinic. A rapid diagnosis provided by the clinic would be beneficial for patient isolation, infection control and contact tracing.

Considerations for vaccination with smallpox, or even an MPX specific vaccine, are ongoing not only as post-exposure prophylaxis but also as a pre-exposure measure among at risk groups such as patients on HIV pre-exposure prophylaxis (PreP), susceptible healthcare workers in the sector and even among diagnostic laboratory staff handling infectious material. Vaccination may become more routine and widespread as the true burden of MPX becomes more apparent.

Ultimately, the future of this outbreak will be determined by similar questions posed by COVID-19 in March 2020; what the extent of the outbreak is, both worldwide and in the United Kingdom, what the current reproduction number is, the extent (if any) of an animal reservoir, and what strategies will be required to drive it down.

Conflict of interest statement

All views expressed all authors own and express no other conflicts of interest.

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