British Journal of Ophthalmology

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Journal:	*British Journal of Ophthalmology*
Manuscript ID	bjo-2022-322268.R2
Article Type:	Review
Date Submitted by the Author:	28-Sep-2022
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Keywords:	Conjunctiva, Cornea, Epidemiology, Infection, Microbiology

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Keywords: monkeypox, *Orthopoxvirus*, keratitis, conjunctivitis, emerging infections

Word count: 3351

ABSTRACT

The 2022 outbreak of monkeypox is of worldwide significance. There has been a rapid escalation in case numbers despite efforts to contain it and the World Health Organisation has declared it a Public Health Emergency of International Concern. To date, over 51,257 laboratory-confirmed cases have been reported, the majority in non-endemic countries, with 3,279 in the United Kingdom. It is vital for ophthalmologists to understand this disease and the risk it poses.

Human monkeypox is a zoonotic disease caused by the monkeypox virus, a double-stranded DNA virus in the *Orthopoxvirus* genus of the *Poxviridae* family. Other orthopoxviruses include variola (smallpox), cowpox and vaccinia; all of which have significant ocular sequelae. Transmission occurs from an animal reservoir (unknown, likely rodents) to a human host, leading to secondary human-to-human spread. During the recent outbreak, a higher incidence has been found in gay, bisexual or other men who have sex with men.

Clinical diagnosis may be challenging as presentation can mimic common ophthalmic diseases. A thorough history is key to identifying potential cases. Ophthalmic manifestations may include preseptal cellulitis, conjunctivitis and keratitis. The oral antiviral agent tecovirimat, which was developed to treat smallpox, is the mainstay of treatment. Trifluorothymidine (trifluridine) eye drops can be used for ophthalmic involvement. In addition, smallpox vaccines have provided some cross-immunity.

Ocular monkeypox should be managed by infectious diseases specialists, in consultation with ophthalmologists to provide the expertise needed to treat potentially vision-threatening complications. This outbreak highlights the need for healthcare providers to implement appropriate infection control measures and be familiar with the identification and treatment of both cutaneous and ocular disease.

BACKGROUND

Monkeypox is a high threat pathogen of significant public health importance.[1] As of 31 August 2022, 51,257 laboratory-confirmed cases have been reported from 99 countries, 3,279 of these in the United Kingdom (UK).[2] The actual number of cases is likely to be much higher.[3] Within the UK, a high proportion are London residents (81%) and male (99%).[3] Surveys have highlighted the majority identify as gay, bisexual or other men who have sex with men (GBMSM).[4] There is evidence of onward transmission in non-endemic countries and that sexual contact is a factor in transmission.[5]

MONKEYPOX VIRUS

Emergence

Monkeypox is a zoonotic disease caused by the monkeypox virus (MPXV), a double-stranded DNA virus in the *Orthopoxvirus* genus of the *Poxviridae* family. Other orthopoxviruses of clinical relevance are variola (smallpox), cowpox and vaccinia (used in the smallpox vaccine). The similarities between their genomes imply a single common ancestor.[6] MPXV is the foremost orthopoxvirus affecting humans since smallpox eradication in 1980.[7]

Monkeypox was recognised in 1958 as a viral eruption in captive primates in Denmark.[8] The first human case was reported in 1970 in Zaire (now the Democratic Republic of Congo, DRC) and it has remained endemic in Central and West Africa.[9] Prior to 2022, imported human cases outside of Africa were infrequent and it was considered a rare, self-limiting disease. The first outbreak outside of Africa was in the United States of America (USA) in 2003 when 47 people were infected.[10,11] Transmission occurred via wild rodents imported from Ghana, housed near prairie dogs being sold as pets; notably there was no human-to-human transmission.[11] Over the last 10 years the frequency and geographical spread of cases has risen steadily. One speculated explanation is the cessation of the smallpox vaccination programme and the consequent drop in vaccine-derived immunity providing cross-protection against orthopoxviruses.[12,13] Other explanations include more frequent exposure to animal reservoirs due to deforestation, armed conflicts in disease areas, geographic spread by increasingly mobile populations and improvements in surveillance and diagnostic capacities.[13,14]

Phylogenetic analysis has identified two strains, or clades of MPXV: the Congo Basin or Central African (CB/CA) clade and the West African (WA) clade. To minimise negative impacts on countries or regions the World Health Organisation (WHO) have agreed a new nomenclature;[15] CB/CA and WA clades are now respectively known as Clade I and Clade II. Clade II consists of two subclades, with the sublineage responsible for the current outbreak named Clade IIb. To date, all cases in non-endemic countries have been identified as Clade IIb. There have been 15 reported fatalities globally, six of which have occurred in non-endemic countries.[2] Clade IIa, the previously dominant circulating strain in West Africa, is milder in comparison to Clade I, which has higher rates of morbidity, mortality and transmission.[7,16] The fatality rate for Clade IIa is <3% whereas the Clade I is up to 11%.[17,18] Newborns, infants and immunocompromised individuals (e.g. with untreated human immunodeficiency virus (HIV)) have a higher risk of fatality.[19,20] Miscarriage and more severe disease have been reported in pregnant women.[16,21] It is important to note that mortality in different settings may differ substantially.

Transmission

Transmission occurs from an animal reservoir (unknown, thought to be small mammals, likely rodents) to a human host, leading to secondary human-to-human spread. Transmission occurs through close physical contact with infectious lesions or mucocutaneous sores, respiratory droplets (and possibly short-range

aerosols) or contact with fomites on contaminated materials (e.g. bedding, clothing).[16] Poxviruses show high environmental stability and can remain viable for up to 56 days on surfaces, depending upon the temperature and room humidity.[22] As a result, healthcare workers, household members and sexual partners are at greater risk of infection.[23] Placental transmission can occur and shedding via faeces may represent another exposure source.[1,24] Recent papers have suggested a genital reservoir of monkeypox virus[18] and the WHO are investigating reports that MPXV has been found in semen.[25]

Clinical Presentation

The classical clinical picture of monkeypox is similar to that of smallpox, but with some important differences; monkeypox is generally a much milder disease than smallpox. Monkeypox starts with a 1-4 day febrile prodrome with headache, myalgia and fatigue, followed by a centrifugal development of deep, well-circumscribed maculopapular, umbilicated, vesicular, pustular and finally crusted scab lesions. The rash preferentially affects the face and extremities of the limbs but can affect any part of the body, including the oral cavity and conjunctiva.[26] Lesions range in size from 0.5-1cm and can be few to several thousand in number.[24] The incubation period is 5-21 days and patients are presumed infectious from rash onset until skin desquamation.[19] Lesions usually appear at the same time and are monomorphic. Permanent, pitted scarring secondary to bacterial infection is common.[17] Lymphadenopathy is frequent and helps to distinguish it from chickenpox and smallpox.[26]

In the 2022 outbreaks occurring outside of endemic countries in Africa (Clade IIb), patients have presented with milder symptoms and pustules, often without a febrile prodrome. Lesions have emerged at different stages of development, in isolated areas without spreading to other parts of the body and as subtle as one lesion.[3] More severe or numerous lesions may occur at the site of inoculation and many primary lesions have been noted in the anogenital area.[4,20] The route by which humans become infected with MPXV is thought to influence both the severity and the manifestations of disease, although it is not clear if or how this varies according to the infecting clade.[27]

Complications of monkeypox infection include conjunctivitis, keratitis, cellulitis, bronchopneumonia, gastrointestinal involvement, sepsis, encephalitis and neuropsychiatric disorders.[16,28] Severe sequelae are more common in those unvaccinated against smallpox.[16] Frequency of signs and symptoms among the 115 confirmed cases in Nigeria between 2017-2018 (Clade IIa) included; rash (100%), fever (88%), lymphadenopathy (68%), myalgia (63%), sore throat (58%), oral ulcers (35%) conjunctivitis (24%), sensitivity to light (22%), vomiting/nausea (22%).[28]

OPHTHALMIC MANIFESTATIONS

Monkeypox

Ocular manifestations include preseptal cellulitis, conjunctivitis and keratitis, either due to primary viral activity, or secondary bacterial infection. In severe cases, monkeypox infection has led to corneal scarring and vision loss.[12,29,30] Detailed studies of monkeypox-induced loss of vision have not been performed.

A study of 282 monkeypox patients in the DRC between 1980-1985 (Clade I) demonstrated that conjunctivitis and eyelid oedema were common but usually self-limiting.[31] 17% of unvaccinated and 13% of vaccinated patients had lesions on the conjunctiva and eyelid margins. Corneal ulceration was seen in 4% (11/250) of unvaccinated patients. One child was blinded bilaterally and three unilaterally. Corneal opacities resulted in impaired vision in seven further children. Scars deforming eyelids, lips, or nares were seen in 2% of

unvaccinated patients. During an outbreak in 2003 (11 cases) one child sustained a severe conjunctivitis with keratitis, leading to extensive corneal scarring.[12]

Between 2010-2013, the Centres for Disease Control and Prevention collected data on monkeypox cases in the DRC (Clade I) and reported conjunctivitis in 23.1% (68/294) of cases.[29] Where conjunctivitis was reported, there was a higher frequency of other symptoms such as lymphadenopathy, sore throat, mouth ulcers, chills/sweating, fatigue, nausea and sensitivity to light.[29] 47% of cases with conjunctivitis were bed-ridden compared to 16% without.[29] These findings suggest conjunctivitis may be associated with a more severe clinical presentation. The proportion of keratitis was not reported. During the 2017-2018 outbreak in Nigeria (Clade IIa), 24% (28/115) suffered from conjunctivitis but the majority of cases were self-limited.[28] One case of unilateral conjunctivitis was reported in the UK 2018 cluster (3 cases, Clade IIa). A conjunctival swab was polymerase chain reaction (PCR) negative for MPXV and bacterial infection was presumed, which responded to topical chloramphenicol.[18]

Related Orthopoxviruses: Smallpox, Cowpox And Vaccinia

Smallpox

Smallpox was responsible for more than a third of the blindness in Europe prior to immunisation and it was a significant cause of blindness in Africa until as late as the 1960's.[32] Typically, 5-9% of patients developed ocular complications.[32] The virus entered the eye via direct shedding from eyelid lesions or infected fingers touching the eye, and was detected in tears of patients with conjunctivitis.[32,33] Manifestations included eyelid and conjunctival pustules, pre-eruption infiltrates, conjunctivitis, phlyctenules, corneal ulceration, disciform keratitis, iritis (with raised intraocular pressure) and isolated cases of retinitis and optic neuritis.[32] Corneal ulceration was often due to a limbal pustule and was associated with perforation, iris prolapse, hypopyon, staphyloma and endophthalmitis. Scarring resulting in ankyloblepharon was reported.[32] Bacterial coinfection was common in keratitis and was a significant cause of blindness.[32]

Vaccinia

Vaccinia virus was used as a live smallpox vaccine and was instrumental in its eradication. Until the licensure of novel attenuated formulations in 2013, it was still used in laboratory and military personnel.[34] It causes ocular complications but at significantly lower rates to smallpox, approximately 10-20 cases per 1 million immunisations.[32] Infection occurs after accidental autoinoculation of vaccinia virus into the eye from the immunisation site, resulting in eyelid erythema, oedema, pustules and cellulitis.[32] In a study of 348 patients with ocular vaccinia, 6.3% had corneal involvement but no serious sequelae.[35] Corneal complications can include ulcers, disciform keratitis and interstitial keratitis.[32] Topical trifluridine has been used successfully as treatment.[34,36]

Cowpox

Cowpox infections occur after contact with an infected animal, typically domestic cats or rats. Ocular complications are rare but severe. Manifestation is usually limited to cutaneous disease e.g. eyelids and conjunctiva but corneal infiltration leading to opacification has occurred.[37–39] Tecovirimat has been used in ocular cases with good clinical outcome.[40]

DIAGNOSIS

Rapid recognition, diagnosis and reporting of monkeypox are critical to preventing transmission. Diagnosis may be challenging as differentials include herpes simplex virus (HSV), varicella zoster virus (chicken pox and shingles), molluscum contagiosum, enterovirus, measles, scabies, syphilis and bacterial skin infection, all of which are frequently seen in ophthalmic emergency departments.[6,18] A careful history to evaluate risk in

the context of the updated case criteria is essential, including sexual history, travel history, contact with confirmed cases and presence of a rash (see Appendix 1 for UK guidance).[41] Healthcare professionals should stratify risk at the point of triage, to allow immediate and appropriate isolation of possible cases, to minimise contact with staff and other patients.

Laboratory confirmation of monkeypox infection is based on nucleic acid amplification testing using orthopoxvirus-specific real-time or conventional PCR of skin or mucosal lesions.[42] Other appropriate sample types include whole blood, serum, urine, throat swabs and ocular samples (including conjunctival and corneal swabs), which may be tested in confirmed cases to assess which compartments are affected by virus. Within the UK, laboratory testing was initially performed exclusively by the UK Health Security Agency (UKHSA), but some specialist hospital laboratories now are able to provide this service. As a Hazard Group 3 pathogen, it is essential to use personal protective equipment (PPE) and adhere to biosafety regulations during specimen collection and transportation (see Appendix 2).[43]

MANAGEMENT

Ocular monkeypox should be managed by infectious disease specialists in consultation with an ophthalmologist to provide the expertise needed to manage potentially vision-threatening complications. If a patient's first presentation is to an ophthalmic emergency department, it is vital to obtain advice from infectious diseases colleagues. If the diagnosis of ocular monkeypox is uncertain, or a suspected case is awaiting PCR confirmation, standard clinical management should be provided; for example, oral antibiotics in preseptal cellulitis, broad spectrum topical antibiotics in bacterial keratitis, topical and/or oral antivirals in viral keratitis. It is important to note that aciclovir and ganciclovir are ineffective against orthopoxviruses as their spectrum of activity is largely limited to herpesviruses. Aciclovir and ganciclovir are prodrugs that require phosphorylation by viral kinases, predominantly from herpesviruses, to exert their antiviral effect; orthopoxviruses do not catalyse this phosphorylation step sufficiently to activate these compounds.

Antiviral medication

Monkeypox antivirals should ideally be given within clinical trials for collection of standardised clinical and outcome data to increase evidence generation on efficacy and safety and, when not possible, used under expanded access protocols, such as MEURI (Monitored Emergency Use of Unregistered and Investigational Interventions).[16]

Tecovirimat

The mainstay of treatment for orthopoxvirus infection, including ocular complications, is oral tecovirimat (600mg twice daily for two weeks). Tecovirimat acts by inhibiting p37, a major envelope protein in orthopoxviruses, preventing the virus from leaving an infected cell and reducing viral replication.[44] Tecovirimat was first used in December 2018, in a laboratory-acquired vaccinia infection.[45] It was approved in Europe and the UK for the treatment of smallpox, monkeypox, cowpox and vaccinia in January and July 2022 respectively.[44,46] No clinical trials were performed to evaluate tecovirimat efficacy in humans and licensure was based on efficacy in animal challenge studies (using MPXV), alongside safety data, pharmacodynamics and pharmacokinetics studies in humans.[16] In the 2021 UK outbreak (a family cluster) it was administered to one patient; although it was not possible to assess clinical or virological effectiveness, it was well tolerated in the treated individual.[18]

Reported side effects have included headache and nausea. It is a weak inducer of cytochrome P450 and may interact with other medications metabolised through the same pathway.[44] Tecovirimat has been used in ocular cowpox with good clinical outcome.[40] Although animal model data suggest good clinical and

virological responses can occur with 5-7 days of treatment, it is recommended that patients complete 14 days of treatment, as it is not yet known if early cessation may precipitate a rebound in disease. The drug is not widely available, particularly in regions regarded as endemic. In the first two months of the 2022 UK outbreak, tecovirimat was offered to some hospitalised patients with severe monkeypox managed in specialist infectious diseases centres. A randomised controlled trial is underway in the UK to assess its effectiveness at reducing the duration of symptoms and viral shedding in non-hospitalised cases.[47] Randomised controlled trials of treatment in hospitalised patients are being planned elsewhere,[48] particularly in countries where tecovirimat is not licensed for the treatment of monkeypox (only smallpox). In Europe, carefully designed multi-centre observational studies have been launched to study tecovirimat use in hospitalised and non-hospitalised patients with monkeypox.

Cidofovir/brincidofovir

Cidofovir and its prodrug brincidofovir are broad inhibitors of viral DNA polymerase and have demonstrated activity against orthopoxviruses in animal and in vitro studies.[16] There are limited data on their effectiveness in the treatment of MPXV and systemic use has been associated with significant side effects necessitating the cessation of treatment.[18] Notably, prolonged systemic cidofovir treatment in HIV-related cytomegalovirus (CMV) retinitis has been reported as a cause of anterior uveitis with hypotony, which did not normally require interruption of treatment.[49] Brincidofovir was developed as a countermeasure for potential smallpox deliberate release events, and was investigated for treatment of other DNA virus infections but is no longer available commercially. Topical cidofovir has been suggested as a potential therapy but it is largely unavailable.[50]

Trifluridine

Trifluorothymidine (trifluridine) is a nucleoside analogue antiviral that inhibits viral DNA synthesis and can be delivered topically in eye drops at a concentration of 1%. It has in vitro activity against orthopoxviruses, HSV-1, HSV-2 (including aciclovir-resistant HSV strains), CMV and adenoviruses.[51] In the USA, it is used for the treatment of HSV keratitis. It has been used in ocular smallpox and vaccinia.[29,36,52] To date, there are no published reports of its use in ocular monkeypox, but the WHO recommends it as a treatment.[16] Some experts recommend prophylactic therapy to prevent spread to the conjunctiva and cornea if lesions are on the eyelid or adjacent to the eye.[30] The recommended dosing regimen is 1 drop 2 hourly, up to a maximum of 9 drops/24hrs and after re-epithelialisation, 1 drop 4 hourly (minimum 5 drops/24hrs) for 7 days. Treatment should be continued until all periocular lesions have healed, but continuous administration for periods exceeding 21 days should be avoided due to potential ocular toxicity.[53] Trifluridine drops are unlicensed in the UK but are considered an ophthalmic ‘special order’ product so can be prescribed but are not easy to procure.[54]

Steroids

The use of adjunctive topical steroids may be considered to decrease the immune reaction in cases of monkeypox keratitis or iritis. Topical steroids should not be prescribed without concurrent topical antiviral therapy and may prolong presence of the virus in ocular tissue.[30,38]

Antibiotics

Broad-spectrum topical antibiotics should be initiated if bacterial coinfection is suspected, or given as prophylaxis in the presence of corneal ulceration or steroid use. Systemic antibiotics are required in patients with preseptal or orbital cellulitis.[16] Abscesses and necrotising infections that are unresponsive to antibiotics may need surgical debridement and grafting.[3]

Vitamin A

In the malnourished, vitamin A supplements should be provided according to standard recommendations due to the important role it has in both wound healing and eye health.[16]

Vaccination

There is no licensed MPXV-based/derived vaccine but smallpox vaccination (using vaccinia virus) provides protection against orthopoxvirus infections, including an estimated 85% protection against MPXV infection.[55] The vaccine used in Europe is a third generation, attenuated modified vaccinia Ankara (MVA-BN; Imvamune or Imvanex) which has a two-dose administration, given at least 28 days apart with a booster at two years.[55] It is replication-defective so can be used in pregnant and immunocompromised individuals. Although not licensed for monkeypox, the vaccine has been used 'off-label' in the UK.[55,56] In the UK, immunisation is offered as pre-exposure prophylaxis to those at risk including GBMSM individuals and healthcare workers, or as post-exposure prophylaxis for high-risk contacts. Vaccination is recommended within 4 days to prevent or attenuate infection. It has been used up to 14 days post-exposure.[55]

Infection control

In England, monkeypox patients are generally managed by the Airborne High Consequence Infectious Diseases (HCID) Network, and between May and July 2022 most hospitalised cases were managed by HCID Treatment Centres and Specialist Regional Infectious Diseases Centres. In July 2022, HCID status was reviewed and removed for monkeypox caused by the Clade IIb virus (monkeypox caused by Clades I and IIa remains an HCID).[57] Patients must remain in strict isolation until no longer considered infectious;[58] in the 2022 outbreak, most cases to date have isolated at home.[59] Possible or probable cases should be advised to isolate and refrain from close contact with any other persons whilst awaiting specimen results. The use of public transport should be avoided and any skin lesions should be covered. The risk of ocular complications can be reduced with regular hand washing and avoiding touching the eyes while there are any active lesions on the skin. Some authorities advise that contact lenses should not be worn during any stage of infection.[28]

Those that require ophthalmic input will need a video consultation, or if deemed necessary, a face-to-face assessment from an ophthalmologist in an appropriate setting.[60] If patients present to ophthalmic emergency departments with possible/probable monkeypox infection, they should be triaged to an isolation room for assessment. Full PPE should be used when assessing patients; which differs between possible/probable and confirmed cases (see Appendix 2 for PPE guidance).[43]

Any reusable ophthalmic equipment e.g. portable slit lamp, ophthalmic lenses, indirect ophthalmoscope, standard slit lamp must be decontaminated in line with local and national infection control guidance.[43] Specialist ophthalmic approved virucidal chlorine-dioxide based products are recommended to meet infection control standards without damaging devices. There is uncertainty about the precise concentration of chlorine or the amount of risk reduction achieved but consensus is that chlorine is likely to reduce residual contamination and is recommended when thermal or vapourised hydrogen peroxide disinfection is not possible.[43] Discussion with Infection Prevention and Control (IPC) teams is essential in establishing local protocols for decontamination.

CONCLUSIONS

Monkeypox is an emerging health threat, with rapidly growing case numbers in a global population with little immunity. The current outbreak highlights the need for healthcare providers to be familiar with the identification of monkeypox, to ensure strict infection control measures are implemented and timely treatment provided. Discussion with IPC teams is recommended to establish local protocols in preparation

for potential ocular monkeypox cases, notably for the cleaning of specialist ophthalmic equipment and to ensure clinicians are not inadvertently exposed to virus during examination.

It is essential that ocular monkeypox patients are jointly managed by infectious diseases specialists and ophthalmologists. There is limited information on ocular monkeypox but the literature will develop as more cases are observed and reported. Research is needed to optimise treatment strategies and allow development of guidelines for clinical management and therapeutics. High quality outbreak data collection is urgently needed to improve our understanding of this neglected disease.

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Contributorship Statement

AM conceived and designed the article and prepared the first draft. SK and JD critically revised and edited the manuscript. All authors had access to and approved the final version for submission. All authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Acknowledgments, Competing Interests, Funding: none declared

APPENDIX

Appendix 1: UKHSA Case definitions as of 9 August 2022.[41]

Possible case A possible case is defined as anyone who fits one or more of the following criteria**:**
A febrile prodrome† compatible with monkeypox infection, where there is known prior contact with a confirmed case in the 21 days before symptom onset †Febrile prodrome consists of fever ≥ 38°C, chills, headache, exhaustion, muscle aches (myalgia), joint pain (arthralgia), backache, and swollen lymph nodes (lymphadenopathy).
An illness where the clinician has a suspicion of monkeypox, such as unexplained lesions, including but not limited to: • genital, ano-genital or oral lesion(s) – for example, ulcers, nodules • proctitis – for example anorectal pain, bleeding

Probable case A probable case is defined as anyone with an unexplained rash or lesion(s) on any part of their body (including genital/perianal, oral), or proctitis (for example anorectal pain, bleeding) and who:
Has an epidemiological link to a confirmed, probable or highly probable case of monkeypox in the 21 days before symptom onset **OR**
Identifies as a gay, bisexual or other man who has sex with men (GBMSM) **OR**
Has had one or more new sexual partners in the 21 days before symptom onset

Actions on a possible or probable case

Test for monkeypox (using designated testing pathway).

Take travel history: if patient reports a travel history to West or Central Africa in the 21 days before symptom onset please discuss with the imported fever service, as these patients may need to be managed as having a high consequence infectious disease. Undertake additional contemporaneous tests to rule out alternative diagnoses if clinically appropriate and if not done already.

If admission of patient required for clinical reasons, admit to single room isolation at negative or neutral pressure at local hospital site with respiratory protective equipment (RPE) and personal protective equipment (PPE) (with appropriate IPC arrangements).

Or, if patient not requiring admission for clinical reasons: self-isolation at home (based on assessment by the clinician and following UKHSA guidance).

Or, if patient not requiring admission for clinical reasons but self-isolation at home is not possible for social or medical reasons following clinician assessment: isolation in single room at negative or neutral pressure at local hospital site with RPE and PPE pending test result (prioritise probable cases).

Highly probable case

A highly probable case is defined as a person with an orthopoxvirus PCR positive result in 2022 and where monkeypox remains the most likely diagnosis.

Confirmed case

A confirmed case is defined as a person with a laboratory-confirmed monkeypox infection (monkeypox PCR positive) in 2022.

Action on a confirmed or highly probable case

All confirmed or highly probable cases should be assessed for the need for admission based on either clinical or self-isolation requirements. The NHS provides guidance on management of patients with confirmed monkeypox.

All confirmed or highly probable cases should be notified to the local health protection team by the clinician.

Appendix 2: Minimum PPE for Monkeypox cases. [43]

Possible/probable cases	Confirmed cases
Gloves	Gloves
Fluid repellent surgical facemask (if LRTI then FFP3)	Fit-tested FFP3 respirator
Apron	Long sleeved, fluid repellent, disposable gown
Eye protection (if there is splash risk)	Eye protection

For possible, probable or confirmed cases, attending ambulatory healthcare (for example outpatients, emergency departments, urgent care centres, general practice, sexual health clinics), patients should be placed in a single room for assessment. The patient should be provided with a fluid repellent surgical facemask. If monkeypox is considered likely and the patient is referred to a HCID unit, the room should not be used before appropriate decontamination.

Responses to Reviewers' comments to authors:

Dear Editorial team,

Many thanks for the Reviewers' comments. We present our individual responses *in italics* to each comment below and have uploaded the revised manuscript in clean and tracked changes versions.

Reviewer: 1

Page 2, line 11: 'or' that ….?

It was not immediately clear what this comment refers to, we suspect it is regarding the term "gay, bisexual or other men who have sex with men (GBMSM)". This is the commonly used and accepted English terminology, so we have not altered the text here.

Page 2, line 50: Does this imply that the mortality of the current outbreak is 0.03% (51257/15)? If so, we are lucky in a way that it isn't Clade 1 or IIa, or is this more an affect of the population involved, etc? Worth a mention?

As an emerging infection the picture is still rapidly evolving and we did not include a reference to a case fatality rate as this has not been clearly defined as yet. We make reference in the text to the likelihood that resource setting may impact outcomes including case fatality rates. It is not yet clear if Clade IIb is less virulent than Clade IIa. This question would be best addressed through epidemiological and virological research and we do not think it is in the remit of our paper to speculate. We have provided the raw figures and relevant references for the interested reader.

Page 3, line 39 and subsequently. If the severity is clade-specific, can the identification of the predominant clade in these outbreaks be provided? Are there similar data yet for the recent outbreak?

The locations of the historical outbreak data are provided, thus inferring their clade. We have added their clades to the text, for absolute clarity.

Regarding the recent outbreak, we did not have any clinical data at the time of submission. There are now case series available but nothing specific to ophthalmology. We do not think that the late addition of references at this stage would change the conclusions of the paper or benefit the reader.

Page 7, line 7: Please specify if there are specific MPXV vaccines available or in development?

*Thank you, for clarity we have included the phrase, "**There is no licensed MPXV-based/derived vaccine but smallpox vaccination (using vaccinia virus) provides protection against orthopoxvirus infections, including an estimated 85% protection against MPXV infection."***

There are a handful of vaccines at pre-clinical stages of development. We have not made reference to these because they are not of clinical relevance at this point in time.