Clinical features and management of individuals admitted to hospital with monkeypox and associated complications across the UK: a retrospective cohort study

Douglas L Fink, Helen Callaby, Akish Luintel, William Beynon, Helena Bond, Eleanor Y Lim, Effrossyni Gkrania-Klotsas, Jospeh Heskin, Margherita Bracchi, Balram Rathish, Iain Milligan, Geraldine O'Hara, Stephanie Rimmer, Joanna R Peters, Lara Payne, Nisha Mody, Bethany Hodgson, Penny Lewthwaite, Rebecca Lester, Stephen D Woolley, Ann Sturdy, Ashley Whittington, Leann Johnson, Nathan Jacobs, John Quartey, Brendan AI Payne, Stewart Crowe, Ivo AM Elliott, Thomas Harrison, Joby Cole, Katie Beard, Tomas-Paul Cusack, Imogen Jones, Rishi Banerjee, Tommy Rampling, Specialist and High Consequence Infectious Diseases Centres Network for Monkeypox, Jake Dunning*

Summary

Background The scale of the 2022 global mpox (formerly known as monkeypox) outbreak has been unprecedented. In less than 6 months, non-endemic countries have reported more than 67 000 cases of a disease that had previously been rare outside of Africa. Mortality has been reported as rare but hospital admission has been relatively common. We aimed to describe the clinical and laboratory characteristics and outcomes of individuals admitted to hospital with mpox and associated complications, including tecovirimat recipients.

Methods In this cohort study, we undertook retrospective review of electronic clinical records and pathology data for all individuals admitted between May 6, and Aug 3, 2022, to 16 hospitals from the Specialist and High Consequence Infectious Diseases Network for Monkeypox. The hospitals were located in ten cities in England and Northern Ireland. Inclusion criteria were clinical signs consistent with mpox and MPXV DNA detected from at least one clinical sample by PCR testing. Patients admitted solely for isolation purposes were excluded from the study. Key outcomes included admission indication, complications (including pain, secondary infection, and mortality) and use of antibiotic and anti-viral treatments. Routine biochemistry, haematology, microbiology, and virology data were also collected. Outcomes were assessed in all patients with available data.

Findings 156 individuals were admitted to hospital with complicated mpox during the study period. 153 (98%) were male and three (2%) were female, with a median age of 35 years (IQR 30–44). Gender data were collected from electronic patient records, which encompassed full formal review of clincian notes. The prespecified options for data collection for gender were male, female, trans, non-binary, or unknown. 105 (71%) of 148 participants with available ethnicity data were of White ethnicity and 47 (30%) of 155 were living with HIV with a median CD4 count of 510 cells per mm³ (IQR 349–828). Rectal or perianal pain (including proctitis) was the most common indication for hospital admission (44 [28%] of 156). Severe pain was reported in 89 (57%) of 156, and secondary bacterial infection in 82 (58%) of 142 individuals with available data. Median admission duration was 5 days (IQR 2–9). Ten individuals required surgery and two cases of encephalitis were reported. 38 (24%) of the 156 individuals received tecovirimat with early cessation in four cases (two owing to hepatic transaminitis, one to rapid treatment response, and one to patient choice). No deaths occurred during the study period.

Interpretation Although life-threatening mpox appears rare in hospitalised populations during the current outbreak, severe mpox and associated complications can occur in immunocompetent individuals. Analgesia and management of superimposed bacterial infection are priorities for patients admitted to hospital.

Funding None.

Lancet Infect Dis 2023; 23: 589–97

Published Online December 22, 2022 https://doi.org/10.1016/S1473-3099(22)00806-4

See Comment page 516

*Members are listed in the appendix (pp 6–17)

Department of Infectious Diseases, Royal Free London NHS Foundation Trust, London, UK (D L Fink PhD, A Luintel MRCP, J Dunning PhD); **Division of Infection and Immunity, University College London, London, UK** (D L Fink, J Dunning); **Rare and Imported Pathogens Laboratory, UK Health Security Agency, Porton Down, Wiltshire, UK** (H Callaby MRCP, T Rampling DPhil); **Department of Infectious Diseases, Belfast Health and Social Care Trust, Belfast, UK** (W Beynon MRCP, H Bond MRCP); **Department of Infectious Diseases, Cambridge University Hospitals, Cambridge, UK** (E Y Lim PhD, E Gkrania-Klotsas PhD); **Department of HIV/GUM, Chelsea and Westminster Hospital, London, UK** (J Heskin MBChB, M Bracchi MD); **Department of Infectious Diseases, Guy's and St Thomas' NHS Foundation Trust, London, UK** (B Rathish MRCP, G O'Hara DPhil, Iain Milligan FRCPath); **Department of Infectious Diseases, St Mary's Hospital, Imperial College Healthcare NHS Trust, London, UK** (S Rimmer MRCP, J R Peters MRCP); **Department of Sexual Health and HIV, King's College Hospital NHS Foundation Trust, London, UK** (L Payne MRCP, N Mody MBBS); **Department of Infectious Diseases, Leeds Teaching**

Introduction

Mpox (formerly known as monkeypox) in humans was first detected and reported in the Democratic Republic of the Congo in the early 1970s.[1] The disease is caused by infection with an orthopox DNA virus, monkeypox virus (MPXV). Two different strains of MPXV are endemic in Africa, with clade I predominant in central African regions and clade II predominant in western African regions.[2] Until the 1990s, both clades caused mostly sporadic cases and outbreaks of disease, with zoonotic transmission.[3] After discontinuation of smallpox vaccination, which also protects against mpox, mpox incidence increased in Africa.[4,5] Outbreaks of human mpox emerged in the Democratic Republic of the Congo in 1996 and in Nigeria in 2017, with evidence of human-to-human transmission, including in urban areas.[6,7]

Hospitals NHS Trust, Leeds, UK (B Hodgson MRCP, P Lewthwaite FRCP); **Tropical and Infectious Diseases Unit, Liverpool University Hospitals NHS Foundation Trust, Liverpool, UK** (R Lester PhD, S D Woolley MD); **Department of Infectious Diseases, London North West University Healthcare NHS Trust, UK** (A Sturdy MRCP, A Whittington MRCP); **Department of Infectious Diseases, North Manchester General Hospital, Manchester, UK** (L Johnson MBChB, N Jacobs BMBS); **Department of Infection and Tropical Medicine, Newcastle-upon-Tyne Hospitals NHS Foundation Trust, UK** (J Quartey MBChB, B Al Payne FRCP); **Department of Infectious Diseases, Oxford University Hospitals NHS Foundation Trust, Oxford, UK** (S Crowe MRCP, I A M Elliott DPhil); **Department of Infectious Diseases, Sheffield Teaching Hospitals NHS Foundation Trust, Sheffield, UK** (T Harrisson MBChB, J Cole PhD); **Department of Infection, University Hospital Southampton NHS Foundation Trust, Southampton, UK** (K Beard MBBS, T-P Cusack MRCP); **Infection Care Group, St George's University Hospitals NHS Foundation Trust, London, UK** (I Jones MRCP, R Banerjee MRCP); **Hospital for Tropical Diseases, Division of Infection, University College London Hospitals NHS Foundation Trust, London UK** (T Rampling); **Pandemic Sciences Institute, Nuffield Department of Medicine, University of Oxford, Oxford, UK** (J Dunning)

Correspondence to: Dr Douglas Fink, Department of Infection and Immunity, University College London, London NW3 2PP, UK
douglas.fink@nhs.net

See Online for appendix

Research in context

Evidence before this study

We searched PubMed from Jan 1, 2017, to Oct 31, 2022, for studies published in English on patients admitted to hospital with monkeypox (mpox), severe mpox, and mpox complications using the following keywords: "(monkeypox) AND (hospitalised OR hospitalisation OR complication OR severe)". Since March, 2022, more than 67 000 cases have been reported worldwide. Monkeypox virus (MPXV) clade IIb has emerged as the likely dominant driver of the current outbreak transmitted predominantly through sexual contact and disproportionately affecting gay and bisexual men who have sex with men. There are no dedicated representative studies of individuals admitted to hospital with mpox or associated complications during the current outbreak. A single national report of hospitalised cases referred to the USA Centre for Disease Control and Prevention Severe Monkeypox Investigations Team and described high mortality (21%) in a highly selected population with high prevalence of advanced HIV infection. Two national retrospective studies in Nigeria during the largest MPXV clade II outbreak reported case fatality rates between 6% and 12·5%, with most deaths occurring in neonates and people living with HIV. Epidemiological and virological factors make the findings of these studies difficult to extrapolate to the populations most affected by the current outbreak. There are no therapies of proven efficacy for human mpox infection. Tecovirimat is an orthopoxvirus envelope protein inhibitor developed for the treatment of smallpox in the context of a deliberate release incident. It is approved for the treatment of mpox in several countries, but studies reporting effectiveness or safety and tolerability in acutely unwell individuals with mpox are unavailable.

Added value of this study

We report the first representative, national-level analysis of individuals admitted to hospital with severe mpox and associated complications in a high-income country. Our retrospective analysis reports cases managed by the UK Specialist and High Consequence Infectious Diseases Network for Monkeypox across 16 centres in ten cities. We describe clinical and laboratory features, including virological data, representing the first such report for a hospitalised cohort, some of whom received treatment with tecovirimat. We report no deaths, but severe pain and secondary bacterial infection were experienced by more than half of the analysis population. We report two cases of encephalitis, five cases of severe ocular complications, and ten cases that required surgical intervention, predominantly for debridement or drainage of secondary bacterial skin and soft tissue infections. More than a third of the analysis population experienced deranged liver function tests during hospital admission. 38 individuals received tecovirimat with early cessation in four individuals, including in two individuals with hepatic transaminitis.

Implications of all the available evidence

Although we report no deaths, we highlight the substantial burden of complex morbidity in immunocompetent individuals admitted to hospital with mpox. Based on few data in selected populations, advanced HIV infection and other causes of severe immunocompromise might significantly increase morbidity and case fatality. Further prospective studies are required to identify risk factors associated with severe mpox and specific complications. Our data suggest that secondary bacterial infection is common, and that studies of anti-microbial prophylaxis and treatment are required in individuals diagnosed with mpox. Tecovirimat appears to be well tolerated, although randomised controlled trials are required to establish effectiveness in preventing and treating severe disease and complications. Further studies are also needed to identify causes of hepatic dysfunction in patients with mpox.

Before 2022, recognised cases of mpox were rare outside Africa and mostly linked to travel to or arrival from Nigeria.[8,9] In May, 2022, several countries in multiple geographic regions reported cases of MPXV infection, primarily in individuals without history of travel to African countries. By September, 2022, more than 67 000 laboratory-confirmed mpox cases had been reported in 106 countries, including more than 3600 cases in the UK.[10] Unlike previous outbreaks in countries with zoonotic reservoirs in Africa, close contact during sexual activities was identified as the dominant route of transmission in the 2022 global outbreak caused by Clade IIb MPXV.[11] Men who are gay or bisexual and other men who have sex with men (GBMSM) have been disproportionately affected, with locally acquired community transmission (particularly sex-associated transmission) predominant in all affected countries.[10,12]

Monkeypox is generally self-limiting. The classical description of mpox is an initial prodromal phase with variable influenza-like symptoms, followed by the development of widespread, characteristic skin lesions which evolve and eventually crust over, dry, and fall off, typically within 14 days.[11] Clinical manifestations seen in the 2022 global outbreak have been linked to sexual transmission routes, with most patients experiencing lesions that are focused, more abundant or more severe in genital, ano-rectal and oropharyngeal regions, possibly reflecting exposure of these areas to high levels of the virus during sexual intercourse.[11–13] In previous outbreaks, hospital admission and increased mortality have been linked to patients' immune status, infection in infancy, and infection with clade I MPXV.[6,14–16] Secondary bacterial infection at sites of skin or mucosal lesions and extra-cutaneous disease, including ocular disease, pneumonitis, and encephalitis have been described in

case series.[14] Globally, 7·8% of cases in the current outbreak have required hospital admission for medical care and sometimes infection control purposes. Crude estimates suggest an overall mortality rate below 0·05%[10] for clade IIb disease, although 21% mortality was reported in a highly selected population with high prevalence of advanced HIV infection in the single available national-level study of individuals admitted to hospital with mpox in 2022. Tecovirimat, an orthopoxvirus envelope protein inhibitor developed for treatment of smallpox in the context of a deliberate release incident, is approved for the treatment of mpox in several countries and regions.[17] Tecovirimat appears to be well tolerated in humans and is efficacious in animal models of mpox,[8,17–19] but data on effectiveness in treating human mpox is unavailable.

In 2022, most UK patients with severe mpox requiring inpatient care were admitted to High Consequence Infectious Diseases (HCID) Centres, Specialist Regional Infectious Diseases Centres, and other hospitals with specialist infection services. These hospitals formed a virtual clinical network to manage the placement of patients, share information and experiences, and discuss case management including treatment options. The network was developed around the National Health Service England Airborne HCID Network, which has provided care to patients admitted to hospital with mpox since 2018.[8]

Monkeypox is an emerging infection and cases were rare in the UK and other countries outside Africa before 2022; therefore, there is a need to share experiences of managing more severe disease. This multi-centre, retrospective analysis aims to report the clinical, laboratory, and virological features of the majority of patients who required in-hospital care for mpox in England and Northern Ireland and describes clinical management including tecovirimat use in a proportion of cases.

Methods

Study design and participants

In this retrospective cohort study, all national clinical network hospitals that managed patients admitted to hospital with mpox were invited to perform local service evaluations of their inpatient mpox care. 16 centres across ten cities in England and Northern Ireland submitted data between May 6, and Aug 3, 2022. These data were collated and form the basis of this analysis. All individuals had clinical signs consistent with mpox and MPXV DNA detected from at least one clinical sample by PCR testing done at the UK Health Security Agency Rare and Imported Pathogens Laboratory (RIPL) or at local laboratories using RIPL-validated testing from July, 2022. Hospital admission was defined as admission to any ward bed for an indication related to management of mpox or associated complications, or a period of more than 24 h spent in an emergency department bed space with review by an infection specialist. Patients admitted solely for isolation purposes were excluded. If a patient was admitted for isolation initially but developed complications during their stay, they were included in the analysis. Each contributing centre followed its local policy for reviewing a proposed service evaluation and a request to submit deidentified data, extracted from inpatient records, for the purposes of a network analysis, without obtaining specific consent from individual patients. Local records were accessed only by clinicians involved in care of patients admitted to hospital at each centre. For cases in which local policy required written approval or registration of a service evaluation, this was obtained by the respective centre. Deidentified data were securely transferred by each centre to the coordinating site (Royal Free Hospital, London, UK) for collation and analysis.

Procedures

Each centre accessed patient case records to populate a deidentified spreadsheet developed by the network. The spreadsheet was designed to capture data typically recorded during routine clinical care and was not part of a research protocol. Clinical data were collected by all core co-authors, who provided care to the patients at each clinical centre, and included clinical histories and outcomes, observations, drug histories, and laboratory results. Data were collected for the duration of hospital admission. Indication for admission and tecovirimat initiation was reported as the principal single indication thought to be most clinically important by the reviewing clinician. Clinical sexual histories were not collected as these generally do not form part of inpatient case records. Peak and nadir values from testing performed during each patient's hospital stay were collected for routine biochemistry and haematology results. Microbiology data were collected across the duration of the hospital stay and sexually transmitted infection results from onset of symptoms (ie, community testing) until hospital discharge. Because this was not a prospective research study, availability of data was dependent on what was routinely recorded in hospital case records and laboratory results systems at each centre. Cycle threshold (Ct) values for both MPXV PCR and orthopox PCR, for all anatomical sites sampled, were included in reports sent by UKHSA to centres; these results were also included in the analysis. We report orthopox PCR results only for our analyses because, unlike MPXV results, they are available for samples. Analyses of orthopox PCR results organised by anatomical site reflected sample labelling at each centre. Samples reported as lesion are thought to reflect skin lesion swabs but might also include a smaller number of mucosal lesion swab samples. For interhospital transfers, the receiving site contacted all other hospitals involved in the single admission episode to ensure data collected were representative and to avoid duplication.

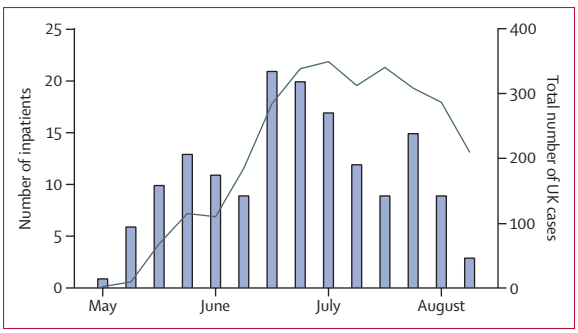

Figure 1: **Number of individuals admitted to collaborative group hospitals compared with total number of cases in the UK by week during the analysis period**
Bars indicate hospital admissions and the line graph indicates the total number of cases.

UKHSA technical briefings provided data for total number of reported mpox cases.[20]

Categorical variables for indications for hospital admission and for tecovirimat initiation were informed by patient management discussions that took place at virtual meetings of the clinical network. Secondary bacterial infection was defined as any clinical or laboratory-confirmed diagnosis at any anatomical site during admission that required antibiotic treatment of any duration. Tonsillitis was defined as sore throat and acute enlargement or erythema of any tonsil. Severe pain was defined as pain requiring analgesia consistent with the third step of the WHO pain ladder (morphine, fentanyl, oxycodone, buprenorphine, oxymorphone, methadone [if increased from maintenance dose]). Immunosuppression was defined by criteria described in the Green Book.[21] Deranged liver function was defined by any abnormal liver function test including bilirubin, alkaline phosphatase (ALP) and alanine transaminase (ALT). High ALT was defined as greater than 50 IU/L for men and greater than 35 IU/L for women, high ALP as greater than 130 IU/L, and high bilirubin as greater than 21 µmol/L. A completed course of tecovirimat was defined as having received 600 mg tecovirimat twice daily for 14 days.

Statistical analysis

The primary outcome of the study was mortality. Secondary outcomes were admission to intensive care, any surgical procedure, duration of hospital admission, secondary bacterial infection, severe pain, and deranged liver function. Pre-specified exploratory analyses were undertaken between orthopox PCR Ct values and duration of symptoms and key blood tests (C-reactive protein, white cell count, and ALT). All outcomes were assessed in all patients with available data. Categorical variables were expressed as frequency and percentage. Continuous variables were summarised as median values and IQR if non-normally distributed and as mean with SD if normally distributed, as indicated. Wilcoxon Rank-Sum test was used for analyses of non-normally distributed qualitative data. Tests of significance were done for median lowest orthopox Ct value between anatomical sites. Correlation analyses were done for each anatomical site between orthopox Ct value and duration of symptoms and named blood tests. For correlation analyses, Pearson correlation coefficient with 95% CI for normally distributed data and Spearman correlation with 95% CI for non-normally distributed data were used. All tests had a significance threshold of 0·05. Data were analysed in Stata software (version 14) and Prism Graphpad software (version 8).

Role of the funding source

No funding.

Results

156 individuals were admitted to 16 network hospitals for inpatient management of complicated mpox during the study period (figure 1). Seven of these individuals were discharged and then readmitted during the study period. 11 inpatients were transferred to network hospitals after admission to hospitals outside of the network, and 14 inpatients were transferred between hospitals within the network to enable safe use of appropriate isolation rooms. 153 (98%) of 156 participants were male and three (2%) were female. Most identified as GBMSM (139 [90%] of 155 with available sexual orientation data) and were of White ethnicity (105 [71%] of 148; table 1). Nearly a third of the study population were people living with HIV (47 [30%] of 155) of whom 85% (40 of 47) had suppressed HIV-1 viral loads and normal CD4 T-cell counts (table 1). The prevalence of significant co-morbidities was low in the study population although ten (6%) of 156 individuals had history of severe immunosuppression, including three people living with HIV with CD4 counts less than 200 copies per mL, five individuals receiving biologic therapy, and two patients receiving immunosuppression for solid organ transplants.

Severe rectal or perianal pain was the most common indication for hospital admission (44 [28%] of 156; table 2). Rates of intercurrent sexually transmitted infections across anatomical sites were high in the study population with nearly a third having laboratory-confirmed gonorrhoea, chlamydia, or herpes simplex virus infections diagnosed during the interval between symptom onset and hospital discharge (table 2). One individual was diagnosed with primary HIV infection at the time of admission. Median intervals between symptom onset and diagnosis (6 days [IQR 4–9]), and symptom onset and hospital admission (7 days [IQR 5–10]), were similar with 46% of individuals diagnosed with MPXV infection on the day of or after hospital admission (72 of 156). Severe pain was common during hospital admission (89 [57%] of 156), as was clinical diagnosis of secondary bacterial infection (82 [58%] of 142; table 2).

	Number of participants (n=156)
Age	35 (30–44)
Gender	
Male	153 (98%)
Female	3 (2%)
Trans or non-binary	0
Sexual orientation*	
Gay men, bisexual men and other men who have sex with men	139/155 (90%)
Heterosexual men	13/155 (8%)
Heterosexual women	2/155 (1%)
Ethnicity or race	
White	105 (67%)
Black	12 (8%)
Latinx	11 (7%)
South Asian	6 (4%)
Other	14 (9%)
Unknown	8 (5%)
HIV status	
HIV positive	47/155 (30%)
On antiretroviral therapy	41/47 (87%)
Most recent HIV-1 viral load <200 copies per ml	40/47 (85%)
Median CD4 cells per mm^3	510 (349–828)
No CD4 cell count in preceding 12 months	12/47 (26%)
CD4 cell count <350 cells per mm^3	9/47 (19%)
Viral hepatitis infection	
Hepatitis B surface antigen positive	3/112 (3%)
Hepatitis C virus antibody positive	2/116 (2%)
Hepatitis C virus RNA positive	0
Reported history of smallpox vaccination	
Ever	3 (2%)
During current pandemic before diagnosis	2 (1%)
Charlson comorbidity index (median, range)	0 (0–8)
Immunosuppression at time of infection	10 (6%)

Data are n (%), n/N (%), or median (IQR), unless otherwise indicated. Differing denominators reported are due to missing data. *Data for one bisexual woman are not presented in the table.

Table 1: **Demographic and clinical background of individuals admitted to hospital with monkeypox virus infection**

	Number of participants (n=156)
Indication for admission	
Severe rectal or perianal pain	44 (28%)
Oropharyngeal symptoms	
Upper respiratory tract disease affecting swallowing or airways	16 (10%)
Throat pain without affecting swallowing or airways	2 (1%)
Secondary bacterial infection	
Non-genital cellulitis	5 (3%)
Genital cellulitis	16 (10%)
Tonsillitis	9 (6%)
Other or not recorded	10 (6%)
Sepsis	0
Urological not secondary to secondary infection	
Difficulty passing urine or urinary obstruction	9 (6%)
Severe genital pain	8 (5%)
Genital oedema	8 (5%)
Ocular or periocular disease	5 (3%)
Encephalitis	0
Extensive and progressive cutaneous disease	14 (9%)
Mental health	0
Other	10 (6%)
Diarrhoea or haematochezia	3/10 (30%)
Fever and myalgia	2/10 (20%)
Acute kidney injury	1/10 (10%)
Dyspnoea	1/10 (10%)
Management of renal replacement therapy	1/10 (10%)
Reduced mobility	1/10 (10%)
Syncope	1/10 (10%)
Laboratory-confirmed concurrent sexually transmitted infection	
Gonorrhoea or chlamydia or herpes simplex virus	43 (28%)
Gonorrhoea	20 (13%)
Chlamydia	15 (10%)
Chlamydia and gonorrhoea	5 (3%)
Herpes simplex virus	16 (10%)
Rectal or perianal	6/16 (38%)
Throat	3/16 (19%)
Genital	2/16 (13%)
Other or unknown	5/16 (31%)
Syphilis	17 (11%)
Time intervals	
Interval between symptom onset and diagnosis, days	6 (4–9)
Interval between symptom onset and admission, days	7 (5–10)
Interval between diagnosis and admission, days	1 (4)
Other	
Severe pain during admission	89 (57%)
Secondary bacterial infection during admission	82/142 (58%)

Data are n (%), n/N (%), median (IQR), or mean (SD). Differing denominators reported are due to missing data.

Table 2: **Indications and characteristics for admission to hospital**

Half of all bacterial throat swabs yielded organisms compatible with clinical pharyngitis or tonsillitis (9 [50%] of 18; appendix p 3). Non-toxigenic *Corynebacterium diphtheriae* (*C diphtheriae*) was isolated from a single throat swab sample in a patient with clinical tonsillitis. A single episode of bacteraemia (*Escherichia coli*) was detected among 49 individuals who had blood samples cultured (1 [2%] of 49). Antibiotic use was high in the study population with 76% (119 of 156) receiving any antibiotics during admission and 51% (79 of 156) receiving intravenous antibiotics, the majority of which were continued for more than 48 h (54 [68%] of 79; table 3). Individuals with clinical

	All (n=156)	Secondary bacterial infection (n=82)	No secondary bacterial infection (n=74)
HIV positive	47/155 (30%)	19 (23%)	28 (38%)
Severe immunocompromise	10 (6%)	5 (6%)	5 (7%)
Peak lesion count			
0–10	52/152 (34%)	29 (35%)	23 (31%)
11–100	81/152 (53%)	42 (51%)	39 (53%)
>100	19/152 (13%)	10 (12%)	9 (12%)
Systemic symptoms			
Lymphadenopathy	102/153 67%	65 (79%)	37 (50%)
Myalgia	49/155 (32%)	27 (33%)	22 (30%)
Reported fever symptoms	109, 70%	65 (79%)	44 (59%)
Fever at admission	41/155 (26%)	28 (34%)	13 (18%)
Peak temperature, °C (n=153)	37·3 (36·9–38·0)	37·4 (37·0–38·3)	37·2 (36·9–37·8)
NEWS at admission (n=155)	1 (0–2)	1 (1–2)	1 (0–1)
Peak haemoglobin, g/L (n=142)	149 (138–155)	151 (139–156)	145 (136–153)
Peak white blood cells, cells ×10⁹/L (n=142)	9·1 (7·4–11·7)	10·2 (7·8–13·2)	8·7 (7·0–10·4)
Neutrophils	5·4 (3·9–7·0)	6·2 (4·1–8·42	6·2 (4·1–8·42
Lymphocytes	3·1 (2·1–3·9)	3·1 (2·3–4·2)	3·0 (1·9–3·7)
Peak platelets, cells ×10⁹/L (n=142)	267 (222–374)	266 (219–404)	271 (222–351)
Nadir platelets, cells ×10⁹/L (n=142)	218 (10–576)	210 (184–264)	225 (200–265)
Peak C reactive protein, cells mg/L (n=139)	58 (18–99)	66 (32–117)	41 (10–76)
Peak creatinine, µmol/L (n=142)	85 (75–98)	85 (73–93)	88 (76–104)
Peak bilirubin, µmol/L (n=139)	8 (6–10)	9 (7–12)	8 (5–10)
Peak ALT, IU/L (n=132)	43 (26–119)	55 (28–150)	35 (24–70)
Peak ALP, IU/L (n=136)	86 (67–109)	89 (67–115)	84 (66–108)
Received any antibiotics	119 (76%)	81 (99%)	38 (51%)
Received intravenous antibiotics	79 (51%)	65 (79%)	14 (19%)
Single dose	6/79 (8%)	2/65 (3%)	4/14 (29%)
<48 h duration	19/79 (24%)	18/65 (28%)	1/14 (7%)
>48 h duration	54/79 (68%)	45/65 (69%)	9/14 (64%)
Received oral antibiotics	106 (68%)	71 (87%)	35 (47%)
Single dose	4/106 (4%)	0	4 (5%)
<48 h duration	10/106 (9%)	6 (7%)	4 (5%)
>48 h duration	92/106 (87%)	65 (79%)	27 (36%)
Received tecovirimat	38 (24%)	23 (28%)	15 (20%)
Surgical procedures	10 (6%)	9 (11%)	1 (1%)
Duration of admission, days	5 (2–9)	7 (3–10)	4 (2–8)

Data are n (%), n/N (%), or median (IQR), unless otherwise indicated. Differing denominators reported are due to missing data. NEWS=National Early Warning Score (an aggregate score of respiratory rate, oxygen saturation, systolic blood pressure, level of consciousness, and temperature). ALT=alanine transaminase. ALP=alkaline phosphatase.

Table 3: **Clinical and laboratory features in individuals admitted to hospital with monkeypox virus infection, by secondary bacterial infection status**

diagnoses of secondary bacterial infections were more likely to have lymphadenopathy (65 [79%] of 82 *vs* 37 [50%] of 74), documented fever at admission (65 [79%] of 82 *vs* 44 [59%] of 74), and higher early warning scores at admission (median 1 [IQR 1–2] *vs* median 1 [0–1]; table 3). However, duration of hospital admission and results of routine blood tests were not substantially different between individuals with or without secondary bacterial infection (table 3). A single patient was admitted to a high dependency unit for monitoring during the study period and a single patient with pre-existing end-stage renal failure received renal replacement therapy as an inpatient. Two individuals were diagnosed with MPXV-associated encephalitis during hospital admission, with orthopox DNA detected in cerebrospinal fluid by PCR; one of these two patients also developed transverse myelitis, and both recovered to their pre-admission clinical status. Five individuals had ocular complications of mpox including four with conjunctivitis, two of whom had peri-orbital cellulitis. Ten (6%) of 156 individuals required surgical procedures for complications related to MPXV infection (appendix p 2). Overall, the median duration of hospital admission was 5 days (IQR 2–9; table 3). 44 (28%) of 156 patients had inpatient stays of 7–13 days and 22 (14%) patients had inpatient stays of 14 days or more. There were no deaths during the study period.

The Ct values from orthopox PCR testing were lower for skin lesion samples (n=134) than for blood (n=28), throat swab (n=44), or urine (n=27) samples, but not significantly different from rectal swab samples (figure 2). An increase in throat orthopox PCR Ct values, possibly reflecting a fall in viral load and reduced viral replication, were correlated with duration of symptoms, which was not the case for results from other anatomical sites (appendix p 3). Conversely, rectal swab orthopox PCR Ct values inversely correlated with systemic markers of inflammation C-reactive protein and white cell count, unlike results from other anatomical sites (appendix p 4).

38 (24%) of 156 individuals received tecovirimat. The median time to tecovirimat initiation was 11 days (IQR 9–12) from symptom onset and 3 days (2–5) from diagnosis (table 4). Intractable rectal or perianal pain (not controlled with analgesia alone) was the single most common indication for tecovirimat initiation (seven [18%] of 38; table 4). The proportion of individuals living with HIV (42% *vs* 26%) or severe immunosuppression (13% *vs* 4%) were higher in the tecovirimat treated group than in those individuals not receiving tecovirimat (table 4). For all sample sites, median Ct values were comparable between those who received tecovirimat and those who did not (table 4). Four individuals stopped tecovirimat treatment early (<14 days): one out of patient choice, one due to rapid treatment response, and two due to suspected adverse events (deranged liver function tests). One dose of cidofovir was also given to one individual with encephalitis.

Of individuals with blood test results available, 35% (47 of 136) had abnormal blood liver function test results during their admission. Deranged liver function was more common in individuals who received antibiotics (40 [34%] of 119) than those who did not receive antibiotics (seven [19%] of 37), and was also more common in individuals who received tecovirimat

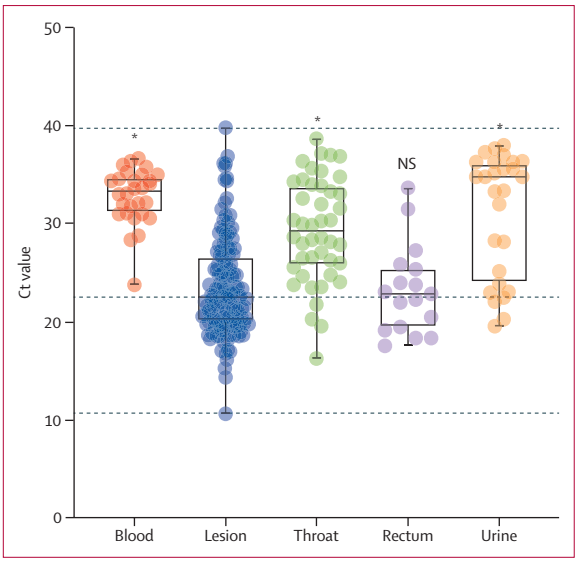

Figure 2: **Orthopox PCR cycle threshold values by anatomical site**
Median and IQR shown in line and box plots. Minimum and maximum values shown by whisker plots. Lesion values were used as the reference for comparisons. NS=not significant (p=0·15). *p<0·0001.

(17 [45%] of 38) compared with in those who did not receive tecovirimat (30 [25%] of 118; table 4). Higher ALT levels were recorded for individuals who received antibiotics (51 [88%] of 58) than for individuals who did not receive antibiotics (51 [68%] of 75). We identified no clear association between ALT and peak viral load across all anatomical sites measured by orthopox PCR (appendix p 5).

Discussion

We describe a retrospective observational analysis of 156 individuals admitted to 16 hospitals across ten cities in the UK with severe mpox or complications of mpox. Representative data on patients admitted to hospital and descriptions of their management are scarce. Our analysis supports most global estimates that overall mortality in mpox caused by clade IIb virus is low.[10] Comparison of our findings with those from other countries is challenging for many reasons, including differences in study designs, virus clades, available health-care resources, and background health at the population level. By contrast to available studies of clade II outbreaks in Nigeria and USA, we did not identify fatal outcomes in our cohort which might, in part, be due to higher rates of severe immunosuppression (particularly advanced HIV infection) in these cohorts.[6,16,22]

Similar to studies of patients not admitted to hospital, we found that observed clinical phenotypes, particularly anogenital or oropharyngeal disease, reflect presumed or confirmed sexual transmission routes in GBMSM individuals.[11,12] Almost a third of our study population had intercurrent sexually transmitted infections, which is higher than that reported for outpatient populations.

	All (n=156)	Tecovirimat (n=38)	No tecovirimat (n=118)
Interval between symptom onset and tecovirimat, days	..	11 (9–12)	..
Interval between diagnosis and tecovirimat, days	..	3 (2–5)	..
Indication for tecovirimat			
Rectal or perianal pain	..	7 (18%)	..
Ocular or periocular disease	..	6 (16%)	..
Upper respiratory tract involvement affecting swallowing or airways	..	6 (16%)	..
Urological	..	6 (16%)	..
Extensive cutaneous disease	..	5 (13%)	..
Rectal abscess or fistula formation	..	2 (5%)	..
Severe immunocompromise	..	3 (8%)	..
Encephalitis	..	2 (5%)	..
Other	..	1 (3%)	..
HIV positive	47/155 (30%)	16 (42%)	31/117 (26%)
Severe immunocompromise	10 (6%)	5 (13%)	5 (4%)
Lowest orthopox PCR Ct value			
Blood (n=38)	33·4 (31·3–34·8)	32·7 (31·8–35·3)	33·7 (31·0–34·6)
Blood negative	9/38 (24%)	3/17 (18%)	6/21 (29%)
Lesion (n=134)	22·6 (20·0–26·8)	21·6 (19·7–25·9)	22·9 (20·2–27·5)
Throat (n=44)	29·3 (25·8–34·0)	28·5 (25·4–33·2)	30·2 (26·0–34·4)
Rectum (n=17; median, range)	22·9 (19·5–25·4)	22·5 (22·0–22·9)	23·1 (19·2–25·9)
Urine (n=27; median, range)	34·8 (23·9–36·3)	34·8 (28·2–36·3)	30·2 (23·9–35·6)
Duration of admission, days	5 (2–9)	7 (6–14)	4 (2–8)
Deranged liver function	47/136 (35%)	17 (45%)	30/98 (31%)
Early cessation of tecovirimat	..	4 (11%)	..
Adverse effect	..	2/4 (50%)	..
Rapid response	..	1 (25%)	..
Patient preference	..	1 (25%)	..

Data are n (%), n/N (%), or median (IQR), unless otherwise indicated. Differing denominators reported are due to missing data.

Table 4: **Clinical characteristics in individuals admitted to hospital with monkeypox, by tecovirimat treatment status**

Pain control is a key clinical management priority for individuals diagnosed with mpox and pain requiring strong opioid analgesia at some point during admission was common amongst patients. We report two cases of MPXV encephalitis; both cases were treated with tecovirimat and had recovered to their normal baseline by the time of hospital discharge. One individual experienced necrotising conjunctivitis and has persistent visual impairment. More detailed descriptions of these cases will be submitted for publication separately by network members. One individual was admitted with dyspnoea but had normal chest radiography, and no episodes of pneumonitis or myocarditis were reported in our analysis, despite these having been described in other studies of mpox.[12,14] Reported secondary bacterial infection was common; no individuals required organ support although surgical management was indicated for skin, soft tissue, or ocular complications in ten individuals. Antibiotic use exceeded 76% for patients and

might have been associated with abnormal liver function tests. Prospective studies of antimicrobial therapy in MPXV-infected individuals are warranted to assess outcomes and complications, along with studies to determine whether clinically diagnosed superinfection in this setting is caused by bacteria, MPXV, or both, particularly given that orthopox infections can disrupt skin microbiota and immune homoeostasis.[23]

Our study is the first to report biochemistry data for multiple individuals receiving tecovirimat for the treatment of mpox. The individuals treated with tecovirimat were predominantly not immunocompromised as immunosuppression alone is not an indication to commence treatment according to the UK interim clinical policy statement on tecovirimat use in patients admitted to hospital. Clinicians stopped tecovirimat treatment early for two patients due to concerns over hepatic transaminitis, although causality was not established. Cessation rates in larger published studies of outpatient populations receiving tecovirimat for mpox were low, but laboratory liver function tests were not reported.[18,19] Transaminitis was common in our patients; antibiotic and analgesic use was common and might account for some of the liver function test abnormalities recorded, and mpox itself might cause hepatitis.[24,25] Unfortunately, we were unable to obtain liver biochemistry results before diagnosis of mpox. Our report emphasises the challenge of determining whether deranged liver function is due to the infectious process or anti-infective drugs administered, including novel antivirals. Further prospective studies with biochemistry outcomes are required to better characterise any relationship between mpox and hepatitis in addition to randomised control trials of tecovirimat. Our analysis was not designed to measure the clinical or virological effectiveness of tecovirimat, and most individuals did not receive sufficient longitudinal sampling to support a descriptive analysis of orthopox PCR results before, during, and following tecovirimat treatment. Further studies are required to establish the efficacy and role of tecovirimat for treatment of severe mpox.

The proportion of our study population living with HIV (30%) is comparable to the proportion reported for outpatients diagnosed with mpox.[11,12,26] Similar to populations in other reported studies, most people living with HIV in our study population had well-controlled HIV infection with normal CD4+ T-cell counts. Limited to available parameters and small patient numbers, there were no clear differences in disease phenotype between people living with HIV and HIV-negative individuals, including for people living with uncontrolled HIV. Further prospective studies are required to better understand MPXV acquisition risk and the natural history of mpox in people living with HIV, and in individuals with different immunosuppression conditions.

The retrospective observational nature of our analysis is its major limitation. In the UK, the absolute number of hospital admissions of individuals with mpox or associated complications is unknown. The network represents the majority of infectious disease centres in England where more than 90% of mpox cases have been diagnosed and severe cases managed; therefore, we expect our data to be representative of typical cases admitted to hospital in the UK. Accepting that our data are incomplete for the UK, we estimate that approximately 5–6% of UK individuals with confirmed or highly probable mpox were admitted to hospital with severe or complicated infection during the study period (156 of 2923).[17] We did not collect data to report the timing of microbiology sampling and antibiotic use, which might have confounded rates of bacteraemia in our analysis. Throat swab sampling in our population was biased by oropharyngeal symptoms, so the clinical significance of identified organisms is also difficult to interpret. We did not record the use of specialist bacteriology procedures for laboratory processing of throat swabs at different centres, therefore the relevance of a single isolate of non-toxigenic *C diphtheriae* is uncertain in an individual without clinical diphtheria. The limited number of individuals with longitudinal virology samples, and the challenge of re-sampling single lesion sites in individuals with high lesion counts, mean that we can infer little about the value of MPXV DNA quantification in disease stratification or prognostication.

Our analysis of a large population of individuals admitted to hospital with mpox and associated complications in the UK serves as salutary reminder that although mild in the majority of those infected, clade IIb mpox can cause a variety of complications in immunocompetent adults that often require multidisciplinary inpatient management. We believe our specialist clinical network approach helped optimise inpatient care and knowledge-sharing for this emerging infectious disease in the UK. Our observations support the need for prospective studies of individuals with severe disease, including longitudinal sampling for virology and biochemistry analyses, and the need for trials of anti-MPXV therapies and antimicrobials aimed at treating or preventing severe disease.

Contributors

JD and all core authors conceptualised the study. All core authors and all additional authors listed in the appendix contributed to clinical care. All core authors contributed to local data curation. Central data curation was managed by DLF and AL. DLF undertook data analyses. All core authors contributed to interpretation of results. DLF, HC, AL, and JD accessed and verified the underlying data. DLF, AL, IM, and JD developed methodology. DLF and JD coordinated the project. DLF and JD wrote the original draft. All core authors contributed to review, editing, and writing. All core authors and all additional authors listed in the appendix reviewed the final edited manuscript before submission. All authors confirm they had full access to all the data in the study and accept responsibility for the decision to submit for publication.

Declaration of interests

We declare no competing interests.

Data sharing

Patient-level data collected for this study will not be made available for data protection and confidentiality reasons. The data dictionary will be made available to approved researchers and enquiries should be directed to douglas.fink@nhs.net.

References

1 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.

2 Chen N, Li G, Liszewski MK, et al. Virulence differences between monkeypox virus isolates from West Africa and the Congo basin. *Virology* 2005; **340:** 46–63.

3 Heymann DL, Szczeniowski M, Esteves K. Re-emergence of monkeypox in Africa: a review of the past six years. *Br Med Bull* 1998; **54:** 693–702.

4 Rimoin AW, Mulembakani PM, Johnston SC, et al. Major increase in human monkeypox incidence 30 years after smallpox vaccination campaigns cease in the Democratic Republic of Congo. *Proc Natl Acad Sci USA* 2010; **107:** 16262–67.

5 Hatch GJ, Graham VA, Bewley KR, et al. Assessment of the protective effect of Imvamune and Acam2000 Vaccines against aerosolized monkeypox virus in cynomolgus macaques. *J Virol* 2013; **87:** 7805–15.

6 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:** 872–79.

7 Mukinda VBK, Mwema G, Kilundu M, et al. Re-emergence of human monkeypox in Zaire in 1996. *Lancet* 1997; **349:** 1449–50.

8 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; **22:** 1153–62.

9 Reed KD, Melski JW, Graham MB, et al. The detection of monkeypox in humans in the Western Hemisphere. *N Engl J Med* 2004; **350:** 342–50.

10 WHO. 2022 monkeypox outbreak: global trends. 2022. https://worldhealthorg.shinyapps.io/mpx_global/ (accessed Sept 30, 2022).

11 Tarín-Vicente EJ, Alemany A, Agud-Dios M, et al. Clinical presentation and virological assessment of confirmed human monkeypox virus cases in Spain: a prospective observational cohort study. *Lancet* 2022; **400:** 661–69.

12 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.

13 Català A, Clavo-Escribano P, Riera-Monroig J, et al. Monkeypox outbreak in Spain: clinical and epidemiological findings in a prospective cross-sectional study of 185 cases. *Br J Dermatol* 2022; **187:** 765–72.

14 Nalca A, Rimoin AW, Bavari S, Whitehouse CA. Reemergence of monkeypox: prevalence, diagnostics, and countermeasures. *Clin Infect Dis* 2005; **41:** 1765–71.

15 Huhn GD, Bauer AM, Yorita K, et al. Clinical characteristics of human monkeypox, and risk factors for severe disease. *Clin Infect Dis* 2005; **41:** 1742–51.

16 Ogoina D, Iroezindu M, James HI, et al. Clinical course and outcome of human monkeypox in Nigeria. *Clin Infect Dis* 2020; **71:** E210–14.

17 Sbrana E, Jordan R, Hruby DE, et al. Efficacy of the antipoxvirus compound st-246 for treatment of severe orthopoxvirus infection. *Am J Trop Med Hyg* 2007; **76:** 768–73.

18 Desai AN, Thompson GR, Neumeister SM, Arutyunova AM, Trigg K, Cohen SH. Compassionate use of tecovirimat for the treatment of monkeypox infection. *JAMA* 2022; **328:** 1348–50.

19 O'Laughlin K, Tobolowsky FA, Elmor R, et al. Clinical use of tecovirimat (Tpoxx) for treatment of monkeypox under an investigational new drug protocol—United States, May–August 2022. *MMWR Morb Mortal Wkly Rep* 2022; **71:** 1190–95.

20 UK Health Security Agency. Monkeypox outbreak: epidemiological overview, 27 September 2022. 2022. https://www.gov.uk/government/publications/monkeypox-outbreak-epidemiological-overview/monkeypox-outbreak-epidemiological-overview-27-september-2022 (accessed Sept 28, 2022).

21 UK Health Security Agency. Contraindications and special considerations: the green book, chapter 6. https://www.gov.uk/government/publications/contraindications-and-special-considerations-the-green-book-chapter-6 (accessed Oct 3, 2022).

22 Miller MJ, Cash-Goldwasser S, Marx GE, et al. Severe monkeypox in hospitalized patients—United States, August 10–October 10, 2022. *MMWR Morb Mortal Wkly Rep* 2022; **71:** 1412–17.

23 Shmeleva EV, de Agüero MG, Wagner J, et al. Smallpox vaccination induces a substantial increase in commensal skin bacteria that promote pathology and influence the host response. *PLOS Pathog* 2022; **18:** e1009854.

24 Müller G, Meyer A, Gras F, Emmerich P, Kolakowski T, Esposito JJ. Monkeypox virus in liver and spleen of child in Gabon. *Lancet* 1988; **1:** 769–70.

25 Weiner ZP, Salzer JS, LeMasters E, et al. Characterization of monkeypox virus dissemination in the black-tailed prairie dog (Cynomys ludovicianus) through in vivo bioluminescent imaging. *PLoS One* 2019; **14:** e0222612.

26 Patel A, Bilinska J, 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.