
Human Monkeypox Infection - Guidance for Clinicians and Public Health

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Version	Date	Summary
1.5	20/05/2022	Clinical features, transmission pathways, IPC recommendations and vaccination, expanded and updated
1.4	09/09/2021	Clinical features, IPC recommendations and vaccination updated
1.3	07/07/2021	Case definition and clinical features updated
1.2	28/06/2021	Case definition updated
1.1	25/06/2021	Number of UK reported cases updated
1.0	24/06/2021	Initial version

1. Background

Human monkeypox infection (HMI) is a very uncommon, occasionally serious zoonotic disease caused by monkeypox virus (MPXV), a species of *Orthopoxvirus*, which includes variola major (responsible for smallpox), variola minor, vaccinia virus (from which smallpox vaccine is derived) and camelpox. The virus was first isolated from cynomolgus macaque monkeys in a research facility in Copenhagen in 1958. MPXV is a highly pathogenic, enveloped DNA virus - in Ireland it is categorised as a Biosafety Level 3 pathogen. MPXV is endemic to tropical rainforest regions of Central and West Africa. Over the last few years, possibly as a result of waning immunity to smallpox, cases and geographical extent of HMI have been increasing, and relatively regular, extensive outbreaks of HMI in Nigeria and the Democratic Republic of the Congo (DRC) are not uncommon. Nigeria had registered no HMI cases for almost 40 years, when in 2017, an upsurge in human disease was identified, which is currently ongoing. Given that HMI is a re-emerging disease, whose epidemiology is evolving, the WHO has identified MPXV as being the most important human *Orthopoxvirus* infection following the eradication of smallpox in 1979. Although unlikely, cases are sporadically exported from Nigeria, in particular.

2. Natural Hosts and MPXV Variants

MPXV has been isolated from a number of animal hosts in sub-Saharan Africa, including small mammals such as rodents. Little is known about the full range of reservoir hosts or transmission in the wild. A wide range of African mammals, including primates, can become infected with MPXV.

MPXV comprises two geographically distinct clades; a West African variant (WA-MPXV) and a Congo Basin variant (CB-MPXV), which, although producing clinically similar pictures, have different genetic and virulence profiles. Human CB-MPXV infection results in a syndrome characterised by greater levels of viraemia, more severe disease, higher mortality and greater human-to-human transmission. Recent data, however, from outbreaks of WA-MPXV in Nigeria has shown that mortality, severe illness, and human-to-human transmission due to this variant may be increasing.¹

3. Human Monkeypox Infection

HMI is a systemic viral exanthematous zoonosis. MPXV was first identified as a human pathogen in 1970, in an infant in the DRC, who was initially diagnosed with smallpox, as the two diseases can resemble one another. Since then, an increasing number of cases and outbreaks of HMI have been reported, almost exclusively in Africa, with large outbreaks reported recently in the DRC and Nigeria. In 2003 the disease was first reported outside Africa when a cluster of 47 cases in the US was linked to close contact with prairie dogs infected by rodents imported from Ghana. Subsequently, travellers infected in Nigeria have been identified in Israel in 2018, in the UK in 2018, 2019 and 2021, in Singapore in 2019 and in the US in 2021. These travel-related cases have tended to arise in the context of concurrent outbreaks of the disease in Nigeria, the likelihood of importation of cases being related to the extent of circulation within endemic African countries. To date, all HMI cases arising in non-African countries have been caused by the WA-MPXV variant. Information on current HMI outbreaks and cases in Nigeria is available [here](#).

4. Transmission

The majority of HMI cases are infected through direct contact with African wild mammals and consumption of bushmeat. In general, MPXV is not considered to be particularly contagious. WA-MPXV had, in the past been associated with only limited human-to-human transmission, but this is being increasingly reported. CB-MPXV is more infectious.

MPXV enters the body through broken skin (including microscopic breaches), the respiratory tract (via inhalation of large droplets and lesion debris contained in disturbed contaminated bedding materials), and across the mucous membranes of the eyes, nose and mouth, and during sexual intercourse. Transmission among gbMSM has been identified as an effective transmission route. Human-to-human transmission occurs by direct contact with lesion exudate, crust material, lesion scabs, body fluids or contaminated materials such as bedding and clothing, and hand touch surfaces. Inoculation by infected animal bite is a recognised route. Faecal viral shedding may represent another mode of transmission. Human-to-human transmission of MPXV by large respiratory droplet

spread can occur during prolonged face-to-face contact, particularly if the case has pronounced respiratory symptoms, but is considerably less likely to occur than with smallpox. Airborne transmission of MPXV is a recognised, though minor, transmission route – infected nasopharyngeal and tracheobronchial fluid and infected lesion squames have the potential to become aerosolised. In vitro experiments indicate that when aerosolised, MPXV virions retain infectivity potential for more than 90 hours.²

The risk of onward transmission of MPXV following contact with a case depends on the nature and proximity of contact (see Human [Monkeypox Infection - Management of Contacts](#) - Section 2.1 Definition of Contacts, p4). Household members, sexual partners, other close contacts (including some hotel and immediate inflight contacts) and those providing care to a case, including HCWs that were not adequately protected, and other transmission-based measures, have a higher risk of infection. In developed countries, the risk of community transmission is considered low.

Contact with an HMI case can be direct or indirect,³ direct contact significantly increasing the likelihood of transmission:

- *direct contact*: physical contact with an HMI case, case material, lesions and bodily fluids
- *indirect contact*: contact ≤ 1 metres of the case and their personal clinical space, without use of appropriate PPE (for a full description of IPC precautions and appropriate PPE for management of HMI see Section 9 - Infection and Prevention Control, p8).

5. Clinical Features

The incubation period of HMI averages 6–13 days (range 5–21 days). The infectious period begins with the onset of fever^a (or 24 hours before the onset of rash in apyrexial cases), and ends with the final desloughing and drying of the skin lesions. The clinical picture mirrors that of non-haemorrhagic smallpox, but with milder symptoms and a shorter clinical course. Most patients will have a mild, self-

^a For contact tracing purposes, case-patients are considered infectious from 24h before onset of rash.

limiting illness. Some cases may be asymptomatic. The clinical course tends to be more severe in the immunosuppressed and children, especially in the neonate and foetus.

The appearance of the clinical features of HMI can be divided into two phases:

- **Invasion:** The earliest symptom tends to be sudden onset fever (generally $\geq 38.5^{\circ}\text{C}$ – which is present in the great majority of cases - frequently accompanied by rigors), followed rapidly by headache (frequently severe), exhaustion (frequently profound), generalised lymphadenopathy, (which generally coincides with onset of fever), involving posterior auricular, cervical and axillary nodes, and in more severe disease, the inguinal nodes. Backache and myalgia are frequently prominent. Less commonly seen are cough/sore throat, and gastrointestinal symptoms - primarily vomiting and diarrhoea. (NB: cardinal prodromal HMI symptoms in **bold**). Prodromal features frequently appear as a cluster of symptoms, rather than appearing sequentially.
- **Eruption:** Between 1 and 3 (but as many as 5) days following fever onset, the rash will appear. Fever and rash frequently appear concurrently. The lesions - initially maculopapular, pruritic and about 2-5mm in diameter - become vesicular, then pustular and painful, and then umbilicated, before ulcerating, crusting and scabbing (see [here](#) and [here](#) for rash images).^{4,5} The entire cycle - until lesion desloughing - takes between 2 and 4 weeks, depending on severity.

The rash starts initially on the face (and in at least one third of patients, the oral cavity) before rapidly progressing craniocaudally, through the various stages, to become centrifugally distributed. Fever and other prodromal symptoms often subside on the appearance of the rash. Facial rash is present in virtually all cases (where it is generally most dense) while the palms and soles are involved in 75% of cases. The lower arms and legs are frequently involved. Lesion formation in the oral cavity and oropharynx can result in coughing/sneezing, and distressing dysphagia, and if extensive, is associated with a more severe clinical course, as is presence of nausea/vomiting. Oropharyngeal lesions producing coughing and sneezing, can potentially result in aerosolisation of secretions. The presence of five or more smallpox/monkeypox conforming lesions/scabs should lead to suspicion of disease.⁶ In known close contacts under surveillance, the appearance of any rash should lead to suspicion of disease.

Sexually Transmitted HMI: When MPXV is sexually transmitted, patients may not present initially with the classical prodromal fever and rash predominating on the face and extremities. In such circumstances, the rash may begin in the genital or perianal region and/or may initially be localised to the lips and surrounding mouth. The more classical systemic features and rash distribution, may only follow later. In cases that have acquired their disease sexually, the systemic features of fever, exhaustion and headache not be as conspicuous as in the more classical presentation.

Secondary bacterial skin infection is not uncommon, and requires early and aggressive intervention. Severe disease is most likely to be seen in neonates, infants and children and the immunocompromised. Depending on the severity of the disease, skin lesions can vary from a few, to many thousands – with disease severity increasing with increasing numbers of lesions.

HMI can be accompanied by a range of significant medical complications, particularly when due to infection with CB-MPXV. Corneal scarring, with loss of vision can occur in 25% of cases. Pulmonary distress or bronchopneumonia, often appearing late in the course of the illness, frequently accompanies severe disease. There have been occasional reports of MPXV-associated encephalitis.

The HMI case fatality rate depends on the infecting clade, from around 1-3% in the case of infection with WA-MPXV (although significantly higher in cases dually infected with HIV), from 4% to as much as 10% in the case of infection with CB-MPXV, most especially when co-infection with uncontrolled HIV occurs. In developed countries, the mortality rate from HMI is likely to be lower than that seen in African countries. Recent infections involving gbMSM appear to be considerably milder than cases described in the past, although this picture may change as the situation evolves.

6. Clinical Recognition

Recognition of HMI requires a high index of clinical suspicion. Clinical identification of HMI is highly unlikely during the invasion (prodromal) phase, unless the patient is a close contact of an already identified (confirmed or probable) case, or is in a recognised high risk group. In general, sporadic cases will not be identified until characteristic lesions begin to appear on the face (or perhaps for even longer, due to delay in presentation, or confusion with varicella).

The two fundamental features that should immediately arouse suspicion of primary HMI are:

- **Rash:** a characteristically distributed, often highly pruritic rash (conforming to the appearance of a monkeypox rash, see examples [here](#) and [here](#)), having an onset 1-3 (but occasionally as many as 5) days following fever/prodromal symptom onset, that begins on the face (most densely), spreads caudally, having ultimately a peripheral distribution (face, palms, soles, sparing trunk in milder cases).
- **Travel:** Recent travel from an African country known to be endemic for HMI (see map below), or recent contact with animals or bushmeat products originating in endemic African countries.
- **Sexual History:** a history of sexual contact with an HMI case or a person identifying as gbMSM with a labial/genital/perianal rash +/- other prominent symptoms of HMI and with no reported history of sexual contact with an HMI case.

The differential diagnoses of HMI include:

- **Varicella:** is the condition most likely to be confused with HMI, particularly in adults, in whom varicella tends to be more severe. The presence of lymphadenopathy, a pre-or peri-eruptive fever and slower maturation and characteristic distribution of skin lesions are cardinal signs supportive of a diagnosis of HMI. In general, varicella has a shorter and milder prodrome and clinical course, lymphadenopathy is unusual (particularly in adults) and lesions, which tend not to become pustular, usually evolve pleomorphically in a centripetal distribution. Unlike the rash of HMI, in which the lesions evolve at the same time, the lesions of varicella will be of a variety of ages.

- **Herpes Simplex Virus, Early Infectious Syphilis (as well as varicella):** are important differential diagnoses in disease involving gbMSM.
- **Measles:** another important differential diagnosis - coryza and rash would tend to be major differentiating features.
- Others to consider would include staphylococcal and other bacterial skin infections, various oral/mucosal eruptions, other conditions producing lymphadenopathy, scabies, and medication-associated allergies.

NB: Cases coming from West African countries may not have been vaccinated against varicella and measles, increasing the likelihood of these conditions. Moreover, as both are transmitted by the airborne route, initial IPC precautions should be precautionary and conservative to cover the possibility of these conditions (see Section 9 - Infection Prevention and Control, p9).

On clinical suspicion that a patient may have HMI and **Varicella and Measles having been excluded from the differential diagnosis:**

- isolate immediately with standard, contact, and droplet precautions^b
- *(if varicella and measles have not been excluded from the differential diagnosis, isolate immediately and implement [standard, contact and airborne precautions](#)⁷)*
- follow the monkeypox management algorithms on the HPSC website <LINK>
- seek immediate microbiological and infection prevention and control advice
- seek immediate expert virological advice from NVRL
- obtain lesion fluid, lesion roof or dried crust samples for urgent PCR analysis
- lesion fluid should be collected and transported in viral transport medium. If the sample is not transported immediately it should ideally be stored at 4⁰ (four degrees)C
- samples should be transferred urgently to NVRL
- document all healthcare staff/visitors/other patients who have contact with the patient

^b A patient with a range of clinical symptoms such as these and a history of travel to Western or Central Africa should be placed in a negative pressure isolation room (where possible) on airborne precautions until varicella and measles have been ruled out. In the ED (and on the ward) such patients need to be segregated from susceptible people immediately.

- Immediate referral to Public Health (HMI is not a notifiable disease, but report any suspected cases urgently) – do not wait for confirmation
- if HMI is confirmed on PCR, referral should be discussed with staff from the National Isolation Unit.

See [Human Monkey Pox Infection Assessment and testing pathway for use in HIV/STI/ID Clinical Setting](#) for full details on initial case assessment.

7. Laboratory Confirmation

As MPXV viraemia is short-lived, confident laboratory diagnosis is based upon viral identification from lesion fluid, scabs and crusts. Polymerase Chain Reaction (PCR) is the preferred laboratory method given its accuracy and sensitivity. Other serological, culture and histochemical investigations may be appropriate – seek microbiological/virological advice. Initial PCR diagnosis is based upon detection of Orthopox DNA. If detected, the isolate will be assumed to be MPXV. Further definitive characterisation required referral to the Rare and Imported Pathogens Laboratory (RIPL), HAS Porton Down.

8. Treatment

Appropriate supportive care with aggressive treatment of complications forms the basis of effective management of HMI.⁸ There is no specific treatment for HMI. Nor is there a specific vaccine that is fully protective against MPXV. Cross-reactivity with vaccinia virus smallpox vaccine can provide cross-immunity with partial protection against infection and reduction in disease severity, but with waning vaccine-derived immunity, the strength of this protective effect is decreasing. Earlier vaccinia vaccines have suboptimal safety profiles but later vaccines, derived from viral variants that do not replicate within cells, have been approved for use with HMI (see Section 10 - Vaccination – below). The Centers for Disease Control and Prevention (CDC) in the US provides a comprehensive list of possible treatment options for HMI.⁹ Treatment of specific secondary bacterial infection should follow usual guidelines.

9. Infection and Prevention Control

On suspicion that a patient may have HMI, they should be immediately isolated using standard, contact, and droplet^c precautions (bearing in mind previous advice regarding varicella and measles), and IPC advice sought. A risk assessment should be undertaken to determine if any modification of approach is required.

NB: *As the main differential condition – varicella - is highly contagious, a precautionary approach should be adopted initially: placing the patient in a negative pressure ventilation room (if available) with staff wearing FFP2/FFP3 face mask (airborne precautions). Only staff with a clear documented history of having had varicella/measles OR who are fully vaccinated against varicella/measles should care for the patient.*

The level of precautions may be downgraded once the diagnosis and the patient's clinical symptoms are established i.e. not coughing, sneezing, no AGPs being carried out, and the local IPC Team have risk assessed that it is safe to do so.

PPE for HCWs caring for HMI patients should include:

- an impervious, disposable long-sleeved gown
- disposable nitrile gloves
- respiratory protection (FFP2/FFP3 respirator face mask), and
- eye protection (face shield or goggles) for all interactions that may involve contact with the patient or potentially contaminated areas in the patient's environment.¹⁰

A record should be kept of all staff who have had direct and indirect contact with the case including first responders, staff in the Emergency Department and staff who enter the patient's room or have transferred the patient between different hospital areas.

^c A precautionary principle approach should be adopted until Varicella and Measles have been outruled as these conditions are the main differential diagnoses from HMI and both are transmitted by the airborne route

NB: Spread of MPXV by fomites is a recognised transmission route, so environmental decontamination with appropriate cleaning and disinfection agents must be a priority.^d

The risk of environmental contamination increases with the increasing development and spread of skin lesions. The biological material that is most potentially infectious consists of skin lesions, lesion fluid and detached scabs. Inhalation of lesion debris is thought to pose a risk to those changing/handling contaminated bedding material. Bearing this in mind, the extent and severity of lesions as well as the immune competence of a patient with suspected HMI should be considered during the IPC risk assessment, and should influence any decision to downgrade from airborne precautions (negative pressure isolation room) to droplet precautions.

Information on environmental cleaning and decontamination options are available in guidance documents developed by Public Health England (PHE) '[Monkeypox: Guidance for environmental cleaning and decontamination](#)'.

10. Public Health Actions^e

The core, urgent public health control and prevention measures needed to minimise transmission of MPXV involve:

- having a high index of clinical and public health suspicion, especially in cases with a suspicious rash that have recently travelled from an endemic region, have had recent contact with a confirmed or probable case or if an unexplained rash occurs in a member of the gbMSM community
- immediate discussion with duty consultant in HPSC
- immediate identification and early contact tracing of healthcare-related and community contacts, if a diagnosis of HMI is strongly suspected;

^d There is limited data on environmental persistence of MPXV or of variola-type viruses, but there is evidence that vaccinia virus may persist for weeks to months on environmental surfaces.

^e**NB:** some of these actions will need to be run in parallel.

- on confirmation of diagnosis, organising Public Health escalation and establishment of an Incident/Outbreak Control Team to coordinate response;
- early classification of contacts on the basis of exposure and categorisation by the level of surveillance required;
- organising surveillance and quarantine of contacts;
- completion of Case and Contact Surveillance forms;
- determining a strategy of vaccination of contacts (see Vaccination – below);
- in incidents where the source of infection is not immediately apparent, the outbreak investigation should be directed at identifying other potential sources of infection, including 1) sexual transmission between gbMSM,^f 2) unrecognised potential cases that may have introduced infection, 2) contact animals imported from MPXV-endemic areas, or 4) domestic animals that may have had contact with animals imported from MPXV-endemic areas.

See Human [Monkeypox Infection - Management of Contacts](#) for full information on assessment and management of contacts.

11. Vaccination

Vaccinia virus vaccine is partially protective against other Orthopoxviruses - data from African outbreak investigations indicate that smallpox vaccine administered within the previous 15 years can be up to 85% effective in preventing HMI.¹¹ If smallpox vaccine is administered within four days of infection, it can prevent onset or modify the clinical course of HMI. If administered between 4 and 14 days of infection, it can attenuate severity of infection, but to a much lesser degree.

A third-generation smallpox vaccine – Imvanex - developed for individuals for whom previous versions of smallpox vaccine were contraindicated, using Modified Vaccinia Ankara (Bavarian-

^f If case is a member of the gbMSM community having no identifiable source of infection, and there have been no recent gbMSM cases, consider escalation with a view to alerting relevant stakeholders of potential of occult chains of transmission.

Nordic⁸), has been found effective in the management of HMI incidents. The safety profile of Imvanex is more favourable than those of previous generations of smallpox vaccines. It was approved in 2013 by the European Medicines Agency for immunisation against smallpox in adults¹² and was employed in the United Kingdom in 2018 following the identification of an HMI case.⁹ In the US, Imvanex has been specifically licensed for the prevention of HMI.⁸ In HMI other outbreaks outside Africa, certain community and HCW contacts have been offered one of the more modern smallpox vaccines, which have been used off-licence.²

Given this partial protection, post-exposure prophylaxis (PEP) with a single dose of Imvanex (off licence) should be considered for the following categories of contacts:¹³

- a) healthcare workers (including domestic staff, etc) caring for the case,
- b) First Responders and
- c) close contacts, including in outbreak settings.

In addition, consideration should be given to offering staff in specialist infectious disease units involved in the care of confirmed cases, pre-exposure prophylaxis (PeEP) with a single dose of Imvanex.

⁸ <http://www.bavarian-nordic.com>

12. HMI Case Definition

Confirmed Case: A person that has been laboratory confirmed

Probable Case: A person with an unexplained oro/ano-genital lesions or other generalised rash with or without one or more classical symptom(s) of Monkeypox infection[†] since 15th March 2022.

AND ONE OR MORE OF THE FOLLOWING:

- Epidemiological link to a confirmed or probable case of Monkeypox in the 21 days before symptom onset;
- Travel history to West or Central Africa where community transmission of Monkeypox is suspected in the 21 days before symptom onset;
- Is a gay, bisexual or other man who has sex with men (gbMSM).

[†] Acute illness with fever (>38.5C), intense headaches, myalgia, arthralgia, back pain, lymphadenopathy

13. References

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Further information can be obtained from:

- [WHO Outbreak Toolbox](#)
- [ECDC Factsheet for health professionals on monkeypox](#)
- [CDC Monkeypox](#)
- [PHE Monkeypox Factsheet](#)
- [Nigerian National Monkeypox Public Health Response Guidelines](#)
- [Epi-Insight – Monkeypox cases reported in the UK](#)