# Human Monkeypox Infection -
# Guidance for Clinicians and Public Health

## V1.7 13.06.2022

| Version | Date | Summary |
|---|---|---|
| 1.7 | 13/06/2022 | Further refinement of clinical presentation in cases in current outbreak; updated information on contact monitoring |
| 1.6 | 07/06/2022 | Transmission pathways updated, risk group information updated, clinical features expanded, expanded information on vaccination, links to guidance and management pathways added |
| 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. Since May 2022, an upsurge in HMI cases in a wide range of countries (including Ireland), has occurred among those without a travel link to a country where monkeypox is endemic, with many countries reporting that cases in this upsurge were predominantly, though not exclusively, in men who self-identify as gay, bisexual or other men who have sex with men (gbMSM).

## 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 on 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, raising the possibility of MPXV spilling over into endemic mammal populations outside Africa . Subsequently, travellers infected in Nigeria have been identified in Israel in 2018, in the UK in 2018, 2019, 2021 and 2022, 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.

Under the Infectious Diseases (Amendment) Regulations 2022 (S.I. No. 258 of 2022), HMI diagnosed in Ireland is a statutorily notifiable disease.

## 4. Transmission

The majority of HMI cases have, traditionally, been 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,

very especially during the May 2022 upsurge. The CB-MPXV strain is considered to be more infectious than WA-MPXV.

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. In the upsurge of HMI cases seen in Nigeria since 2017, more than 2/3 of cases developed genital infections, indicating the likelihood that MPXV could be transmitted through close skin-to-skin contact during sexual intercourse. In the May 2022 outbreak, sexual contact between gbMSM, has been identified as highly creditable transmission route.

Human-to-human transmission of MPXV 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 likely to be a 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). Household members, sexual partners (particularly gbMSM partners), other close contacts (including some hotel and immediate inflight contacts) and those providing care to a case, including HCWs that were not wearing appropriate PPE, or had not adhered to relevant IPC recommendations, have a higher risk of infection. During the upsurge of cases seen since May 2022, cases have been predominantly, though

not exclusively, among gbMSM. In developed countries, the risk of onward 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 *Interim Infection Prevention and Control Precautions for healthcare workers for Possible or Confirmed Monkeypox*.

## 5. Clinical Features

The incubation period of HMI averages 6−13 days (range 5−21 days). The period of infectiousness lasts for between 3 and 4 weeks. 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. This entire process generally takes between 2 and 3 weeks, but final healing of the skin might take up to 4 weeks. 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-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 ≥38.5°C – which is present in a majority of cases - frequently accompanied by **rigors**), followed rapidly by **headache** (frequently severe), **exhaustion** (frequently profound)**,** generalised **lymphadenopathy,** (which

[a] For contact tracing purposes, case-patients are considered infectious the onset of fever, or in the absence of systemic symptoms, from 24h before onset of rash.

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 and skin healing - takes between 2 and 4 weeks, depending on severity.

Classically, 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, although this is not thought to be a significant transmission route (unless aerosols a produced as a result of AGPs). 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.

**NB - Current Outbreak: In the May 2022 outbreak, cases have tended to be characterised by a modified clinical presentation, in which prodromal features (systemic features, fever, headache, asthenia, myalgia) were less pronounced than those of classical presentation, being frequently absent, or only appearing after the development of the rash. In addition, the rash has tended to differ in a number of ways from the classical rash of HMI, being frequently a) the initial symptom of**

**infection, b) localised initially to the anogenital region and/or the lips and surrounding mouth, c) having a modified appearance, and not necessarily the classical vesciculopapular form, and d) consisting of very few (and sometimes only single) lesions.**

Secondary bacterial skin infection is not uncommon in HMI, 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. Severe cases with high numbers of lesions (<1000) run the risk of becoming dehydrated due to a) transudation of fluid via skin lesions, and b) inability to take fluids by mouth, due to oropharyngeal pain and dysphagia.

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. In the US outbreak in 2003, there were isolated 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. However, the clinical manifestation of disease involving gbMSM appears to be considerably milder, and more circumscribed than cases arising from Africa, due in part to the greater sensitivity of surveillance systems in developed countries.

## 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.

**Differential Diagnoses**

- **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.

- **In gbMSM:** important differential diagnoses would include - Herpes Simplex Virus, early infectious syphilis, scabies and VZV (chickenpox/shingles).
- **In children:** important differential diagnoses would include - VZV (chickenpox/shingles), Herpes Simplex Virus, Enterovirus (Coxsackie/Hand Foot & Mouth), Influenza-like illness.
- **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*.

On clinical suspicion that a patient may have HMI:

- **Immediately implement** all recommended IPC precautions
- Patient should be assessed according the assessment pathway most suitable to clinical setting and age of patient
- Sampling should follow the process outlined in the laboratory transportation plan
- Document all healthcare staff/visitors/other patients who have contact with the patient
- Immediate referral to Public Health (HMI is a notifiable disease, report any suspected cases immediately – do not wait for confirmation
- Cases should, following an individual health risk assessment for severity and risk factors, be clinically categorised as either requiring inpatient care, or being fit for home isolation (the great majority).

In the May 2022 outbreak, significant case numbers, coupled with the relatively minor symptoms seen in many cases, has meant that milder cases require to be, and are suitable for self-isolation at home. There is a range of guidance related to home self-isolation available on the HPSC website.

## 7. Laboratory Confirmation

The most accurate and sensitive method to diagnose MPXV is the detection of MPXV DNA in swabs collected from the lesion or lesion fluid. Viraemia is short-lived and the detection of MPXV DNA in blood is inconsistent.

It is recommended that a swab is collected from the lesion/lesion fluid and placed into viral transport medium (VTM). The swab has to be transported in accordance with current guidance, using a nominated approved courier, to the NVRL. The sample is currently initially processed in a high containment laboratory for downstream PCR testing. The NVRL utilises a range of different assays to identify Orthopox viruses and additional assays to detect, and discriminate between, WA-MPXV and CB-MPXV.

## 8. Treatment

Appropriate supportive care with aggressive treatment of complications forms the basis of effective management of HMI.[7] 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.[8] Treatment of specific secondary bacterial infection should follow usual guidelines.

## 9. Infection and Prevention Control

Full information on the recommended infection prevention and control (IPC) precautions and PPE for the management of possible or suspect HMI cases for is available in the *Interim Infection Prevention and Control Precautions for healthcare workers for Possible or Confirmed Monkeypox*.

On suspicion that a patient may have HMI, they should be immediately isolated in a single room with en suite bathroom facilities (ideally a negative pressure isolation room) using standard, contact, and airborne precautions, and IPC advice sought. A risk assessment should be undertaken to determine if any modification of approach is required.

Appropriate PPE for use during the care/management of suspected/confirmed cases of HMIv includes:

- Respirator Mask: FFP2/FFP3
- Eye protection: Goggles/Visor
- Disposable nitrile gloves
- Impervious Long-sleeved gown

HCW contacts should be identified and recorded as laid out in Monkeypox Infection - Management of Contacts. 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.

**NB**: Spread of MPXV by fomites is a recognised transmission route, waste should be handled as Category A Waste. Environmental decontamination with appropriate cleaning and disinfection agents must be a priority.[b]

[b] 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.

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 and waste management are available in *Interim Infection Prevention and Control Precautions for healthcare workers for Possible or Confirmed Monkeypox*.

## 10. Public Health Actions[c]

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 reporting and 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;
- 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;

[c] Some of these actions will need to be run in parallel.

- Organising surveillance of contacts;
- Completion of Case and Contact Surveillance forms;
- Identification of contacts who should be offered vaccination (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,[d] 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 and Surveillance Forms.

## 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.[9] 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-Nordic[e]), 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 adults[10,11] 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

[d] 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.

[e] http://www.bavarian-nordic.com

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 Imvanex (off licence) should be offered to certain categories of contacts, and pre-exposure prophylaxis for certain categories of HCW. See *Immunisation Guidelines for Ireland* - Chapter 20a Smallpox (variola)/Monkeypox, for full details.

## 12. HMI Case Definition

See the Interim monkeypox case definition.

# 13. References


1. Simpson K et al. Human monkeypox - After 40 years, an unintended consequence of smallpox eradication. *Vaccine*. 2020 Jul 14;38(33):5077-5081. Available at https://www.sciencedirect.com/science/article/pii/S0264410X2030579X?via%3Dihub. Accessed 21/7/21.

2. Verreault D. Susceptibility of monkeypox virus aerosol suspensions in a rotating chamber. *J Virol Methods*. 2013 Feb;187(2):333-7. Available at https://pubmed.ncbi.nlm.nih.gov/23142251. Accessed 18/5/22.

3. Vaughan A et al. Two cases of monkeypox imported to the United Kingdom, September 2018. *Euro Surveill*. 2018 Sep 20; 23(38): 1800509. Available at https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6157091/pdf/eurosurv-23-38-1.pdf. Accessed 7/8/21.

4. Her Majesty's Government. *Guidance – Monkeypox*. Available at https://www.gov.uk/guidance/monkeypox. Accessed 21/6/21.

5. Reed K et al. The detection of monkeypox in humans in the Western Hemisphere. *N Engl J Med*. 2004 Jan 22;350(4):342-50. Available at https://pubmed.ncbi.nlm.nih.gov/14736926/. Accessed 21/6/21.

6. Bunge EM et al. The changing epidemiology of human monkeypox-A potential threat? A systematic review. *PLoS Negl Trop Dis*. 2022 Feb 11;16(2):e0010141. Available at https://pubmed.ncbi.nlm.nih.gov/35148313/. Accessed 18/5/22.

7. Reynolds MG et al. Improving the Care and Treatment of Monkeypox Patients in Low-Resource Settings: Applying Evidence from Contemporary Biomedical and Smallpox Biodefense Research. *Viruses*. 2017 Dec; 9(12): 380. Available at https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5744154/. Accessed 6/7/21.

8. CDC. *Monkeypox: Treatment.* Available at https://www.cdc.gov/poxvirus/monkeypox/clinicians/treatment.html. Accessed 25/5/2i.

9. CDC. *Monkeypox and Smallpox Vaccine Guidance*. Available at https://www.cdc.gov/poxvirus/monkeypox/clinicians/smallpox-vaccine.html. Accessed 6/8/21.

10. Bavarian Nordic. Summary of product characteristics - Imvanex. Kvistgaard: Bavarian Nordic; 2018. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002596/WC500147896.pdf. Accessed 1/9/21.

11. ECDC. *Factsheet for Health Professionals on Monkeypox*. Available at https://www.ecdc.europa.eu/en/all-topics-z/monkeypox/factsheet-health-professionals. Accessed 21/6/21.

Further information can be obtained from:

- HPSC - Monkeypox
- WHO - Monkeypox
- WHO Outbreak Toolbox
- ECDC - Monkeypox
- CDC - Monkeypox
- HSA Monkeypox
- Nigerian National Monkeypox Public Health Response Guidelines