

## ESCMID Emerging Infections Subcommittee (EIS) Commentary on Mpox, 21.08.2024

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## Overview

### About the ESCMID EIS Commentary on Mpox

This ESCMID EIS mpox commentary provides up-to-date, evidence-based information on mpox (formerly known as monkeypox) for healthcare professionals, researchers, and public health officials. This resource is compiled by ESCMID EIS to support the global response to mpox outbreaks.

### Current Global Mpox Situation

As of August 2024, the world is facing a significant mpox outbreak, primarily affecting countries in Central and East Africa, particularly the Democratic Republic of the Congo (DRC) and neighboring countries, with cases reported across several regions. The outbreak is characterized by the sustained human-to-human transmission of the clade I monkeypox virus (MPXV).

In 2023, 14,957 mpox cases, including 739 deaths (CFR: 4.9%), were reported from seven African Union Member States. In 2024, 17,541 mpox cases, including 517 deaths, have already been reported from 12 African countries, representing a major increase compared to the same period the previous year.

### Key Features of the 2024 Outbreak

1. DRC is the epicenter as of August 16<sup>th</sup>, 2024, accounting for 96.3% of all cases and 97% of all deaths reported by 16<sup>th</sup> August, 2024; spread to neighboring countries and declaration of Public Health Emergency of Continental Security by Africa CDC.
2. Emergence of clade Ib MPXV.

3. Declaration of Public Health Emergency of International Concern (PHEIC) by WHO on August 14<sup>th</sup>, 2024.

### Timeline of Significant Events

- **1958:** Mpox virus first isolated from research monkeys in Copenhagen, Denmark.
- **1970:** First human case of mpox recorded in DRC.
- **1980s:** Smallpox vaccination stopped, potentially reducing cross-immunity against mpox.
- **2003:** First human case outside Africa (USA) linked to exotic pet importation.
- **2018:** First imported human cases in UK, Israel, and Singapore.
- **2022:** Unprecedented global outbreak of clade IIb MPXV.
- **2023 mid-September:** Emergence of clade Ib MPXV in Kamituga, DRC.
- **2024, early:** Rapid increase in mpox cases in DRC and neighboring countries.
- **2024, July 25<sup>th</sup> - August 2<sup>nd</sup>:** First reported cases in Rwanda, Burundi, Kenya, and Uganda.
- **2024, August 15<sup>th</sup>:** First cases of clade Ib outside Africa

## Epidemiology

### Global Epidemiological Overview

The current outbreak has seen a significant increase in number of cases, particularly in Africa. In 2023, 14,957 cases and 739 deaths (CFR: 4.9%) were reported from seven African Union Member States. This represents an 80% increase compared to 2022.

In 2024, the situation has further escalated with 17,541 mpox cases, including 517 deaths, reported from 12 African countries. This marks a 160% increase compared to the same period in 2023.

The true number of cases may be higher.

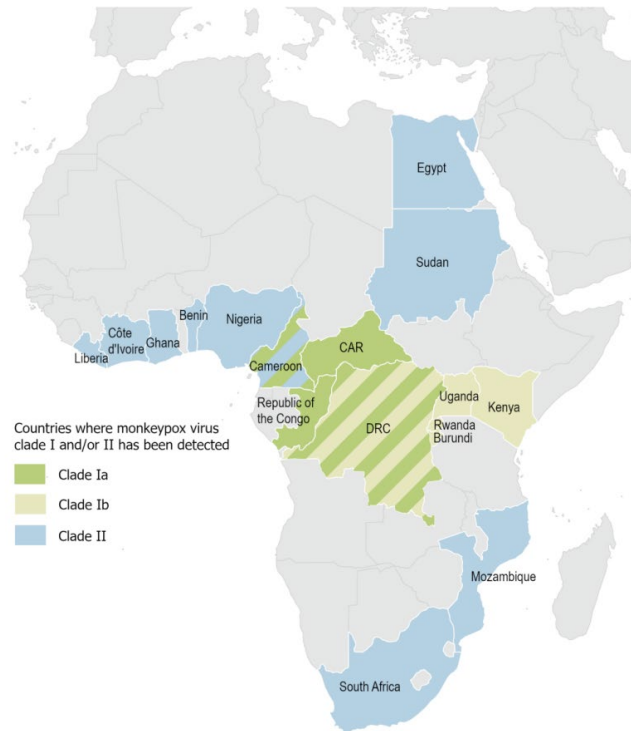
### Outbreak in DRC and Other African Countries

The Democratic Republic of Congo (DRC) is the epicenter of the epidemic, accounting for:

- 96.3% of all cases reported in 2024
- 97% of all deaths reported in 2024

The outbreak has expanded internally among the 26 provinces of DRC and to neighboring countries. Recent cases of clade 1b have been reported in four countries neighboring the DRC that have not reported mpox before:

- Rwanda
- Burundi
- Kenya
- Uganda



**African countries where monkeypoxvirus clade I and/or clade II have been detected (ECDC Risk Assessment report. August 16<sup>th</sup>, 2024)**

### **Factors that Might Be Contributing to Resurgence in East and Central Africa**

1. Close proximity of human populations to wildlife, particularly in rural and forested areas.
2. Deforestation disrupting natural habitats of reservoir animals.
3. Limited health system resources and capacity to monitor and detect mpox outbreaks early.
4. Overall worldwide decline in immunity following smallpox vaccination cessation in the 1980s.
5. Conflicts and political instability causing population displacements.
6. Stigma associated with mpox potentially discouraging individuals from getting tested.
7. Misinformation and misconceptions about mpox.
8. Possible mutations in the virus, potentially increasing its transmissibility.

## **Virology and Pathogenesis**

### **Characteristics of Monkeypox Virus**

The Mpox virus is a double-stranded DNA virus (approximately 200 kilobases) belonging to the Poxviridae family and the Orthopoxvirus genus. It is closely related to the variola virus (smallpox), cowpox virus, and vaccinia virus.

### **Clades and Variants**

Two main clades of MPXV are recognized:

1. **Clade I** (formerly Congo Basin clade):

- Generally associated with more severe illness and higher mortality rates.
  - Endemic to Central Africa.
  - Some outbreaks have had mortality rates up to 10%, although more recent outbreaks have shown lower rates.
2. **Clade II** (formerly West African clade):
- Typically causes milder disease.
  - Endemic to West Africa.
  - IIb has been responsible for the global outbreak that began in 2022 (CFR 0.03%).

The current outbreak involves a novel variant of clade I, designated as clade Ib.

## Recent Phylogenetic Analyses

Phylogenetic studies of the 2024 outbreak have revealed:

- Emergence of clade Ib MPXV, estimated to have originated in mid-September 2023 in Kamituga, DRC.
- Evidence of APOBEC-3 type mutations, indicating adaptation to human hosts.
- Increased human-to-human transmission capability.
- Responsible for the local outbreaks found in South and North Kivu via sustained human-to-human transmission.

## Pathogenesis and Host Immune Response

MPXV infection typically through skin or abrasions or mucosae. The virus replicates at the inoculation site, spreads to local lymph nodes, and then disseminates throughout the body via the bloodstream. The host immune response involves both innate and adaptive immunity, with cell-mediated responses playing a crucial role in viral clearance.

## Clinical Aspects

### Transmission Routes

MPXV can spread through direct contact with infected wild animals, through close contact (including intimate or sexual contact) with a person with mpox, and through contact with contaminated materials.

#### Close or Intimate Contact

-Regardless of type, mpox virus can spread to anyone through close, personal contact, including:

- Direct skin-to-skin contact with mpox rash or scabs from a person with mpox
- Contact with saliva, upper respiratory secretions (snot, mucus), and bodily fluids or lesions around the anus, rectum, or vagina from a person with mpox
- Pregnant people with mpox can pass the virus to the fetus during pregnancy or to the newborn during and after birth.

-Direct contact can happen during intimate contact, including:

- Oral, anal, or vaginal sex, or touching the genitals or anus

- Hugging, massage, and kissing
- Prolonged face-to-face interactions (such as talking or breathing)

#### Indirect contact

Mpox virus can spread to anyone through contact with objects, fabrics, and surfaces that have not been disinfected after use by someone with mpox. It is important to take account of the environment, particularly wastewater, in the spread of the virus.

The contagiousness occurs from the time symptoms start until the rash has fully healed and a fresh layer of skin has formed.

#### Mpox can spread from animals to people in a few ways

Through small wild animals in West and Central Africa, where mpox is endemic, during activities like hunting, trapping, or processing infected wild animals in areas where mpox is endemic. Direct close contact with an infected animal, fluids or waste, or getting bitten or scratched.

People are less likely to get mpox from a pet, but it's possible. Close contact with a pet that is infected, including petting, cuddling, hugging, kissing, licking, and sharing sleeping spaces or food, can spread mpox to a person.

### **Incubation Period**

The incubation period of MPXV ranges from 5 to 21 days, with an average of 6 to 13 days. Some individuals may contract the infection without developing symptoms.

### **Clinical Presentation and average Disease Course**

1. **Prodromal phase (1-4 days):**
  - Fever
  - Malaise
  - Headache
  - Lymphadenopathy (swollen lymph nodes)
  - Myalgia (muscle aches)
  - Sore throat
2. **Rash phase:**
  - Typically begins 1-3 days after fever onset
  - Progression: macules → papules → vesicles → pustules → crusts
  - Rash often starts on face and spreads to other parts of the body
  - Lesions can affect mucous membranes, genitalia, and conjunctiva
  - Lesions in the current outbreak have been reported in the face, trunk, limbs, palms, conjunctival, urethral, penile, vaginal, genital, and ano-rectal areas
  - The main differential diagnoses are chickenpox, but also measles, bacterial skin infections, syphilis, herpes, etc.
3. **Resolution:**
  - Lesions crust over and resolve in 2 to 4 weeks

The disease is often mild and self-limiting, with symptoms usually resolving spontaneously in two to four weeks.

## Complications

Severe systemic forms with multi-organ involvement and higher case fatality rates may happen, mainly in vulnerable groups.

The most frequently observed complications are:

- Secondary bacterial infections
- Pneumonia
- Encephalitis
- Keratitis and corneal ulceration
- Sepsis
- Dehydration and malnutrition (in the absence of supportive treatment)
- Severe systemic forms with multi-organ involvement (in vulnerable groups)
- Vertical transmission, stillbirth (in pregnant people)

## High-Risk Populations for severe disease

- Children under 15 years (in endemic areas, accounting for 68% of reported cases and 85% of fatalities in the 2023 DRC outbreak) specially under 1
- Immunocompromised individuals, particularly those with untreated HIV
- Pregnant people

## Diagnosis

### Specimen Collection and Handling

- Lesion samples (vesicular or pustular fluid, crusts)
- Nasopharyngeal, oropharyngeal or rectal swabs
- Blood samples for serology
- Proper PPE and biosafety measures are crucial during collection and handling

### Laboratory Testing Methods

1. Real-time PCR (gold standard)
  - Requires dedicated research infrastructure and trained personnel
  - MPXV is classified as a risk group 3 (RG-3) pathogen, requiring stringent containment and safety measures
2. Viral culture
3. Electron microscopy
4. Serology (IgM and IgG detection)

Detecting clade Ib cases and sharing sequences are important at the current timepoint.

### Point-of-Care and Rapid Diagnostic Tests

- GeneXpert (Cepheid, U.S.)
- Standard M10 MPX/OPX® (SD Biosensor, South Korea)

Both show promising clinical sensitivity on lesion samples and oropharyngeal swabs for clade I MPXV diagnosis

- Antigen rapid diagnostic tests (AgRDTs)
  - Show high specificity but low sensitivity
  - Clinical efficacy for clade I MPXV screening remains to be investigated

## Treatment

### Supportive Care Strategies

- Fluid and electrolyte management
- Nutritional support
- Pain management
- Wound care for skin lesions
- Management of secondary bacterial infections

### Antiviral Treatments

Drug	Mechanism	Clinical Trials	Comments
<b>Tecovirimat (TPOXX®)</b>	Antiviral: Inhibits viral envelope protein VP37	Phase 2/3/4	<ul style="list-style-type: none"> <li>• Approved in 2022 for the treatment of mpox in U.S. and EU/EEA countries.</li> <li>• Demonstrated therapeutic effects against mpox in animal models.</li> <li>• Safe and well-tolerated in healthy volunteers.</li> <li>• A Swiss-Brazilian collaborative phase III study (UNITY) is currently underway to assess its efficacy in adults and adolescents.</li> <li>• Recent PALM007 trial results (August 15<sup>th</sup>, 2024): Safe but did not improve clade I mpox resolution in DRC.</li> <li>• An EU-funded phase IV clinical trial (EPOXI) is expected to start at the end of 2024.</li> <li>• <b>Dosage:</b> 600 mg twice daily for 14 days (adults)</li> </ul>
<b>NIOCH-14</b>	Antiviral: Inhibits viral envelope protein VP37	Phase 1	<ul style="list-style-type: none"> <li>• Analogue of tecovirimat licensed in the Russian Federation for the treatment of mpox.</li> <li>• Has demonstrated similar effectiveness than tecovirimat in mice models.</li> <li>• Clinical efficacy against mpox is still uncertain.</li> </ul>
<b>Cidofovir / Brincidofovir</b>	Antiviral	Restricted use	<ul style="list-style-type: none"> <li>• Approved by FDA for the treatment of smallpox</li> <li>• Showed in vivo and in vitro antiviral activities against several orthopoxviruses.</li> <li>• No clear benefit in three treated mpox patients in a recent observational study.</li> </ul>
<b>VIGIV*</b>	Human Ig	Restricted use	<ul style="list-style-type: none"> <li>• Considered for emergency use in mpox patients with severe complications or unable to mount an immune response in the U.S.</li> </ul>

			<ul style="list-style-type: none"> <li>• Data on the effectiveness of VIGIV for mpox are lacking.</li> </ul>
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\*Intravenous Vaccinia Immune Globulin

## Management of Complications

- Antibiotics for secondary bacterial infections
- Intensive care support for severe cases
- Ophthalmological care for ocular complications

## Recent Clinical Trial Results

PALM007 Trial (August 2024):

- Randomized, placebo-controlled trial in DRC
- 597 participants with laboratory-confirmed mpox
- Preliminary results: Tecovirimat did not significantly reduce lesion duration
- Overall mortality (1.7%) lower than historical rates, suggesting benefit of supportive care

## Prevention and Control

### Vaccination

#### Available Vaccines

1. MVA-BN (JYNNEOS®/IMVANEX®/IMVAMUNE®)
  - Non-replicating, live-attenuated vaccine
  - Approved for prevention of mpox in many countries
  - Favorable safety profile with mild side effects
2. LC16 (KM Biologics, Japan)
  - Attenuated smallpox vaccine
  - Licensed in Japan for mpox prevention
3. ACAM2000®
  - Replication-competent vaccinia virus vaccine
  - Approved for emergency use in some countries
  - Significant side effects limit its use

#### Vaccination Strategies and Recommendations

WHO Strategic Advisory Group of Experts (SAGE) on Immunization recommends vaccination for:

- Residents of high-risk areas (e.g., rural communities)
- Sex workers, gays, bisexuals, MSM, or individuals with multiple casual sexual partners
- Health workers repeatedly exposed to mpox
- Contacts of mpox patients, including children and household members

#### Vaccine Effectiveness Data

- Two doses of MVA-BN: estimated 66-86% effectiveness in high-risk cohorts
- Single dose: approximately 76% effectiveness
- Post-exposure vaccination: estimated 20% effectiveness

#### Challenges in Vaccine Access and Distribution

- Limited global supply
- Cold chain requirements
- Equity issues in distribution between high- and low-income countries

- Regulatory hurdles in some affected countries
- Limited availability in endemic countries

### Public Health Measures

- Case identification and isolation
- Contact tracing and monitoring
- Risk communication and community engagement
- Enhanced surveillance in affected areas
- Travel advisories and screening at points of entry

### Infection Prevention and Control in Healthcare Settings

- Standard, contact, and droplet precautions
- Appropriate personal protective equipment (PPE)
- Proper handling and disposal of contaminated materials
- Environmental cleaning and disinfection
- Healthcare worker training and monitoring

## Risk Assessments

### ECDC Risk Assessment for EU/EEA

- [Risk assessment: Monkeypox multi-country outbreak](#) (August 16, 2024)

	Likelihood of infection	Impact	Overall risk for the assessed population
<b>In the affected countries</b>			
EU/EEA citizens travelling to the affected countries and having close contact (healthcare workers, household or other close contact and/or multiple sexual contacts) with affected communities or living in the affected countries	High	Low	Moderate
EU/EEA citizens travelling to the affected countries, but not having close contact with affected communities	Low	Low	Low
<b>In the EU/EEA</b>			
Close contacts of possible or confirmed imported cases	High	Low	Moderate
Close contacts of possible or confirmed imported cases with underlying immunocompromising conditions and those with an untreated HIV infection	High	Moderate	High

EU/EEA general population	Very low	Low	Low
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Summary of the risk due to MPXV clade I for the populations under assessment:

- High risk for EU/EEA citizens travelling to affected countries and having close contact with affected communities
- Moderate risk for close contacts of imported cases in the EU/EEA
- High risk for close contacts with underlying immunocompromising conditions and those with untreated HIV infection
- Low risk for the general EU/EEA population

### WHO Situation Reports

- [Multi-country outbreak of mpox, External situation report](#). Edition #35- 12 August 2024

### Africa CDC Assessments

- [Declaration of Mpox as a Public Health Emergency of Continental Security](#) on August 13, 2024
  - Appeal for mobilization of financial, technical, and logistical resources across the continent
  - Emphasis on combating stigma, misinformation, and encouraging case reporting

UK HSA Assessments

[Clade I mpox virus infection - GOV.UK \(www.gov.uk\)](#) Urgent advice for the National Health system, last updated August 16, 2024

[HCID status of mpox \(monkeypox\) - GOV.UK \(www.gov.uk\)](#) Mpox status as a high consequence infectious disease, last updated August 14, 2024

## One Health Perspective

### Animal Reservoirs, Wildlife Interface and Retrozoonotic risk

- MPXV can infect a wide range of mammal species, including:
  - squirrels
  - prairie dogs
  - marmots
  - chinchillas
  - giant-pouched rats
  - monkeys
  - anteaters
  - hedgehogs
  - shrews
- Rabbits at adult age can be infected
- Rats and mice can be possibly infected particularly for newborns
- Infections in gerbils, hamsters, cats and dogs are unknown
- But in these conditions the risk of contamination from humans to animals (retro-zoonoses), particularly in non-endemic areas, cannot be eliminated

## Environmental Factors

- Impact of deforestation and land-use changes on animal habitats
- Potential contamination from human waste in rural areas
- Climate change effects on host-pathogen dynamics

## Resources

### Links to Key Public Health Agencies

- [World Health Organization \(WHO\) Mpox Page](#)
- [European Centre for Disease Prevention and Control \(ECDC\) Mpox Page](#)
- [Centers for Disease Control and Prevention \(CDC\) Mpox Page](#)
- [Africa CDC Mpox Resources](#)
- [UK Health Security Agency HCID status of mpox \(monkeypox\)](#)

## Selected News and Updates

- August 16<sup>th</sup>, 2024: [ECDC risk assessment: Monkeypox multi-country outbreak](#)
- August 15<sup>th</sup>, 2024: (NIH) [The antiviral tecovirimat is safe but did not improve clade I mpox resolution in Democratic Republic of the Congo](#)
- August 14<sup>th</sup>, 2024 (WHO:) [WHO Director-General declares mpox outbreak a public health emergency of international concern.](#)
- August 13<sup>th</sup> 2024 (Africa CDC): [Africa CDC Declares Mpox A Public Health Emergency of Continental Security, Mobilizing Resources Across the Continent](#)

## Selected Publications

- [The untold story of how Nigeria’s mpox outbreak sparked a worldwide epidemic](#) (Cohen J and Tsanii A. Science. August 16<sup>th</sup>, 2024). This article chronicles the mpox outbreak originating in Nigeria in 2017, examining its undetected spread before becoming a global epidemic. It highlights challenges in identifying and addressing the outbreak, including stigma and overlooked sexual transmission, while questioning if earlier intervention could have prevented its worldwide spread.
- Desai, A. N., Koopmans, M., Otter, A., Grobusch, M. P., Jokelainen, P., Atkinson, B., Cunha, F., Valdoleiros, S. R., Preda, V. G., Fusco, F. M., Rovers, C. P., Greub, G., Di Caro, A., Simonsen, L., Ntoumi, F., & Petersen, E. (2024). Implications of the 2023-2024 MPXV clade I outbreak in the Democratic Republic of the Congo to global public health. *Clinical microbiology and infection: the official publication of the European Society of Clinical Microbiology and Infectious Diseases*, 30(9), 1092–1094. <https://doi.org/10.1016/j.cmi.2024.04.016>
- Vakaniaki, E.H., Kacita, C., Kinganda-Lusamaki, E. *et al.* Sustained human outbreak of a new MPXV clade I lineage in eastern Democratic Republic of the Congo. *Nat Med* (2024). <https://doi.org/10.1038/s41591-024-03130-3>.
- Kinganda-Lusamaki E., Amuri-Aziza A., Fernandez N., et al. Clade I Mpox virus genomic diversity in the Democratic Republic of the Congo, 2018 - 2024: Predominance of Zoonotic Transmission. medRxiv pre-print (2024). <https://doi.org/10.1101/2024.08.13.24311951>.

- Branda, F.; Romano, C.; Ciccozzi, M.; Giovanetti, M.; Scarpa, F.; Ciccozzi, A.; Maruotti, A. Mpox: An Overview of Pathogenesis, Diagnosis, and Public Health Implications. *J. Clin. Med.* **2024**, *13*, 2234. <https://doi.org/10.3390/jcm13082234>
- Ghosn, Jade et al. Impact of vaccination with third generation modified vaccinia Ankara and sexual behaviour on mpox incidence in men who have sex with men: analysis among participants of the ANRS-174 DOXYVAC trial. *The Lancet Regional Health – Europe* (2024). <https://doi.org/10.1016/j.lanepe.2024.101020>.

## Q&A

### **Q: What is the current status of the mpox outbreak?**

**A:** As of August 2024, there is a significant outbreak primarily affecting countries in Central and East Africa, with the Democratic Republic of Congo as the epicenter. WHO has declared it a Public Health Emergency of International Concern (PHEIC) on August 14<sup>th</sup>, 2024.

### **Q: What is different about the current outbreak compared to previous ones?**

**A:** The current outbreak involves a new variant (clade Ib) of the monkeypox virus. There are many unknowns about the new variant at the moment.

### **Q: What are the main challenges in controlling this outbreak?**

**A:** Key challenges include limited vaccine access in affected areas, healthcare system constraints in some regions, the potential for further spread through various transmission routes, and the need for increased surveillance and public health measures.

### **Q: How can healthcare professionals best prepare for potential mpox cases?**

**A:** Healthcare professionals should stay informed about the latest developments, familiarize themselves with the clinical presentation of mpox, implement proper infection control measures, and be prepared to quickly isolate suspected cases and initiate appropriate diagnostic procedures.

### **Q: What is the case-fatality ratio for the current mpox outbreak**

**A:** The case-fatality ratio (CFR) for the current mpox outbreak is challenging to determine with precision due to several factors:

1. Sorting: Many mild cases may go unreported, potentially inflating the CFR.
2. Reporting delays: There can be a lag between case identification and outcome reporting, which may temporarily skew the ratio.
3. Varying healthcare systems: Different countries have varying levels of healthcare access and quality, which can impact survival rates.
4. Evolving situation: As the outbreak is ongoing, the CFR may change over time.
5. Limited data: In some regions, data collection and reporting may be incomplete.
6. Differences in affected populations: The CFR may vary depending on factors such as age, underlying health conditions, and access to care.