McMaster University | Health Forum

Living Evidence Profile

Best-available evidence related to the mpox outbreak

30 August 2024

[MHF product code: LEP 6.12]

Context

- Clade I (Congo Basin clade) of the monkeypox (mpox) virus, predominantly found in Central African countries, particularly the Democratic Republic of Congo (DRC), saw a significant surge with over 20,000 cases reported in the DRC by June 2024.
- On 14 August 2024, the World Health Organization (WHO) declared mpox a Public Health Emergency of International Concern due to the rapid spread of clade Ib in the eastern DRC, and in four neighbouring countries that had not previously been affected by mpox.
- The mpox Global Strategic Preparedness Response Plan highlighted the urgent need for proactive measures and research to address critical knowledge gaps.
- We had previously maintained a living evidence profile of the best-available evidence related to the mpox outbreak with 11 versions produced between May 2022 and October 2022 (at which time no further updates were deemed necessary).
- This new update to the living evidence profile was requested to specifically build on this previous work, but with a focus on clade I (including Ia and Ib) monkeypox virus given the outbreaks occurring and the need to identify and profile the available evidence about it.
- The next planned update for this living evidence profile will include evidence on both clades.

Box 1: Evidence and other types of information

+ Global evidence drawn upon

Evidence syntheses selected based on relevance, quality, and recency of search

+ Forms of domestic evidence used (🍁 = Canadian)

Evaluation

Data analytics

*** Additional notable features**

Prepared in the equivalent of three-business days using an 'all hands-on deck' approach

Question

What is the best-available evidence related to the mpox outbreak?

High-level summary of key findings

- We identified 31 evidence documents (seven evidence syntheses, 23 single studies, and one set of slides from a global conference convened at the time of writing this report).
- Clade I mpox virus, historically prevalent in Central Africa, possesses distinct genetic characteristics, including a homolog of the vaccinia virus complement control protein, which may contribute to its increased virulence compared to other clades.
- Clade I monkeypox is being detected as sustained human-to-human transmission, including through sexual contact, with its geographic spread expanding beyond traditional endemic areas in Africa to countries in Europe and Asia.

- Evidence is still emerging, and therefore it is difficult to make conclusions about whether clade Ia and Ib are more transmissible or have worse mortality rates than clade II, so continued research is important.
- However, studies have found that clade Ia primarily affects children (>90% under 15) with higher mortality rates (5–10%) and predominantly facial rashes (82% of cases), while emerging data on clade Ib suggests it mainly affects adults with lower mortality rates (around 0.7%) and predominantly manifests as genital (60–85% of cases) and oral (40% of cases) lesions.
- Vaccinia vaccine, vaccinia immunoglobulin, and antiviral medicines may be used to control an outbreak, alongside the use of personal protective equipment.
- While evidence noted a lack of mpox-specific rapid diagnostic kits, recent advancements include a validated real-time PCR assay (dD14-16) for detecting clade Ib cases and other PCR and genome sequencing techniques to differentiate clade I from other clades, though challenges persist for health professionals to distinguish it from similar diseases like chickenpox in low-resource settings.
- The clinical presentation of clade I typically includes fever, headache, night sweats, myalgia, coryzal illness, and peripheral lymphadenopathy, followed by lesions in mucosal surfaces and skin after one to two days, and while earlier studies suggested a longer incubation period compared to other clades, recent evidence indicates that the incubation period may not be significantly different, averaging 7.3 days (95% CrI 5.0–10.2 days).
- While historical data suggested higher case fatality rates for clade I mpox (approximately 9.8–11%) compared to clade II (3.5% for IIa and 0.1% for IIb), recent evidence indicates more nuanced rates (5–10% for Ia, 0.7% for Ib, 0% for IIa, 3–5% for IIb), with children, young adults, and immunocompromised individuals at greater risk, though these figures may vary based on factors like health care access and comorbidities, and firm conclusions are still emerging).
- There is a lack of completed randomized control trials for mpox therapeutics, though ongoing trials for tecovirimat exist and antiviral medications such as tecovirimat and brincidofovir have been used.

Box 2: Approach and supporting materials

At the beginning of each living evidence profile and throughout its development, we engage a subject matter expert, who helps us to scope the question and ensure relevant context is taken into account in the summary of the evidence.

We identified evidence addressing the question by searching PubMed, Scopus, Europe PC, and SSRN. All searches were conducted on 27 August 2024. The search strategies used are included in Appendix 1. In contrast to synthesis methods that provide an in-depth understanding of the evidence, this profile focuses on providing an overview and key insights from relevant documents.

We searched for full evidence syntheses (or synthesis-derived products such as overviews of evidence syntheses) and protocols for evidence syntheses. We also included published single studies and pre-prints.

We appraised the methodological quality of evidence syntheses that were deemed to be highly relevant using the first version of the AMSTAR tool. AMSTAR rates overall quality on a scale of 0 to 11, where 11/11 represents a review of the highest quality, medium-quality evidence syntheses are those with scores between four and seven, and low-quality evidence syntheses are those with scores less than four. The AMSTAR tool was developed to assess reviews focused on clinical interventions, so not all criteria apply to evidence syntheses pertaining to delivery, financial, or governance arrangements within health systems or implementation strategies.

A separate appendix document includes:
1) methodological details (Appendix 1)
2) overview of the included evidence syntheses and single studies (Appendix 2)
3) details about each identified synthesis (Appendix 3)
4) details about each identified single study (Appendix 4)
5) documents that were excluded in the final stages of review (Appendix 5)
6) references.

This rapid evidence profile was prepared in the equivalent of three days of a 'full court press' by all involved staff.

- Non-randomized studies suggest safety for tecovirimat but potential liver concerns with brincidofovir, though this evidence was of very low certainty.

Framework to organize what we looked for

- Biology
  - Clade I
    - Subclade Ia
    - Subclade Ib
  - Clade II
    - Subclade IIa
    - Subclade IIb
- Epidemiology
  - Transmissibility
  - Geographic spread
  - Protective immunity
- High-risk populations
  - 2SLGBTQI+
  - Children
  - Pregnant people
  - People who are immunocompromised
  - Healthcare workers
  - Other
- Prevention and control
  - Information and education (e.g., including risk communication)
  - Non-pharmaceutical measures to prevent infection
  - Non-pharmaceutical measures to control the spread of infections
  - Pharmaceutical measures used as part of public health strategies
  - Strategies grounded in behavioural science
  - Surveillance and reporting
- Diagnosis
- Clinical presentation
  - Symptom onset and duration
  - Complications
  - Variability in clinical presentation
- Prognosis (e.g., clinical severity, including morbidity and mortality)
- Treatment

What we found

We identified 31 evidence documents relevant to the question, of which we deemed 17 to be highly relevant, eight of medium relevance and six to be of low relevance (see Appendix 1 for methodological details). The identified evidence documents included:

- seven evidence syntheses
- 23 primary studies
- one set of slides from the 2024 Aligning Mpox Research Response with Outbreak Goals – Scientific Conference that was convened at the time of writing this report.

For the high-level profile of key findings presented below based on the literature identified, it is important to note that clade I comprises two distinct subclades, Ia and Ib, which may have important clinical and/or epidemiological

differences. Where possible, we have stratified the data by subclade to provide a more nuanced and informative presentation. However, in cases where the specific subclade was not identified in the original studies, we have reported these findings separately as "clade I (subclade unspecified)."

Coverage by and gaps in existing evidence syntheses and domestic evidence

The identified evidence provides valuable insights into various aspects of clade I mpox, including its biology, epidemiology, prevention and control, diagnosis, clinical presentation, prognosis, and treatment. These evidence syntheses and single studies, which included systematic reviews, observational studies, retrospective descriptive studies, and bioinformatics analysis studies, offer important information on the genetic characteristics, transmission patterns, and severity of clade I infections, particularly in Central African countries.

However, there are still significant gaps in the evidence on clade I monkeypox virus. We identified limited research on effective treatments specifically for clade I mpox, with a notable absence of randomized controlled trials. The effectiveness of existing smallpox vaccines against clade I is not well documented. Additionally, there is a lack of evidence on the long-term health impacts of clade I infections and the socio-economic consequences of outbreaks in affected communities.

While some studies provide information on high-risk groups such as children and immunocompromised individuals, there is insufficient evidence on how clade I differentially affects population subgroups (e.g., children, pregnant people).

Key findings from included evidence documents

Biology

Clade I monkeypox virus, historically prevalent in Central Africa, exhibits distinct biological characteristics that set it apart from other clades.(1) Genomic analysis has revealed that clade I possesses certain genes, such as a homolog of the vaccinia virus complement control protein, which are absent in the West African clade (clade II) and may contribute to its potential for increased virulence.(2) The virus has shown signs of positive selection in genes related to immunomodulation and virulence, suggesting ongoing adaptation to human host immune systems.(3) Clade I has recently evolved to include a novel sub-lineage (clade Ib) in the eastern DRC, demonstrating the virus's capacity for genetic diversification, the virus exhibits diverse sub-populations without clear geographic structuring within the Congo Basin, indicating complex evolutionary dynamics.(4; 5)

Biologically, the incubation period of mpox can vary between clades. While some studies suggest that clade I may have a longer incubation period compared to other clades,(1) recent research indicates that the differences may not be statistically significant. A comprehensive analysis of the 2022 global outbreak and historical data estimated a pooled mean incubation period of 8.1 days (95% CrI 7.0–9.2 days) across all clades. Clade I infections were characterized by a mean of 7.3 days (95% CrI 5.0–10.2 days), whereas clade II infections showed a mean of 8.9 days (95% CrI 6.6–11.7 days). However, these differences were not statistically clear and could be due to sampling variability.(6)

DNA extracted from a single lesion is sufficient to conduct complete genome sequencing of the monkeypox virus strain, allowing for accurate determination of the virus's genetic lineage and potential geographic origin.(7) This genetic analysis capability enhances our understanding of the virus's biology. However, current literature does not provide substantial evidence to differentiate its characteristics from clade I and clade Ib of the monkeypox virus. Further research is needed to elucidate any distinct features of this sub-lineages.

Epidemiology

Clade I monkeypox virus has historically been known for its circulation in southern, forested regions of African countries in the Congo basin, primarily the DRC and Cameroon. This virus has shown increasing prevalence over the past

decade, with recent evidence indicating evolving transmission patterns.(8) The geographic spread of clade I appears to be expanding, with travel-related infections originating largely in Ghana, Côte d'Ivoire, and the DRC, and spreading to other countries.(9) The virus is further divided into subclades Ia and Ib, each with distinct characteristics that have important implications for transmission, demographics, and clinical outcomes.

Historically, clade I transmission has been primarily zoonotic, with high exposure to rodents (91%) and non-human primates (77%) reported before the onset of rash in affected individuals.(10) However, recent evidence indicates evolving transmission patterns, particularly for subclade Ib with sustained human-to-human transmission reported. The current mpox clade I outbreak in 2023–2024 includes over 20,000 cases and 1,000 deaths reported across 25 of 26 provinces by June 2024.(4) It is important to note that a cluster of clade I mpox infections in the DRC was reported to be transmitted through sexual contact, a route previously associated only with clade II.(11) This observation, while based on limited data, suggests a potential shift in transmission patterns that warrants further investigation.

Demographically, clade I mpox affects a wide age range, with a notable burden on children. In the Central African Republic, outbreaks since 2018 have primarily affected forested regions and younger populations, with children under 16 being particularly vulnerable.(12) Similarly, in the DRC, 60% of cases were found in children under 14 years of age.(10) This demographic trend, however, varies between the two subclades, Ia and Ib, which have shown distinct transmission dynamics and affected populations.

Subclade Ia characteristics

Clade Ia, while still predominantly zoonotic with 60–75% of transmissions, has shown an increase in human-to-human transmission, now accounting for 35–40% of cases.(13) This subclade primarily affects children under 15, who make up more than 90% of cases. While the HIV co-infection rate was relatively low (0.6% in a 1998 study), the overall mortality rate ranges from 5–10%, with children being the most vulnerable group and accounting for the majority of deaths. However, under optimal care conditions, as demonstrated in the PALM-007 trial, the mortality rate can be reduced to 1.7%.(13)

Subclade Ib characteristics

As of July–August 2024, new cases of Clade Ib have been reported in several countries, including Burundi (258 cases), Rwanda (4 cases), Uganda (4 cases), Kenya (2 cases), Sweden (1 case), and Thailand (1 case).(13) It is predominantly spread through human-to-human transmission, accounting for 99% of cases, including sexual contact. Clade Ib mainly affects adults, with 85% of cases in the DRC being in this age group. Of these cases, 52% are female, and only 15% are children under 15. The HIV co-infection rate among those with known status was 7%, though it is important to note that the baseline HIV prevalence in the studied population is not specified in the available data. Notably, the mortality rate for Clade Ib is lower at 0.7% compared to clade Ia (5–10%) based on the latest surveillance data.(13)

Of particular importance is that data on Clade Ib is still emerging, and it remains unclear whether findings from Africa will be generalizable to other settings due to a variety of factors. These include behavioural and cultural differences, structural healthcare disparities, variations in healthcare access, nutritional status differences, and the prevalence of co-morbidities across populations. The comparison of results from observational studies in different countries with varying designs, objectives, and standards of care makes it challenging to draw firm conclusions.

This underscores the importance of continued research and surveillance of clade I mpox, particularly as its transmission patterns and geographic distribution continue to evolve.

It is essential to recognize that this discussion is based on an interpretation of the currently available evidence, synthesizing findings from various studies. As more primary research emerges, particularly from diverse geographic and demographic contexts, our understanding of clade I mpox and its global impact may evolve further.

Prevention and control

One recent high-quality evidence synthesis (literature last searched in 2022) noted the use of smallpox vaccine (vaccinia vaccine), vaccinia immunoglobulin, and antiviral medicines can be used to prevent spreading of mpox (all clades).(2) The evidence synthesis reports that smallpox vaccines can be up to 85% effective in preventing infection with the mpox virus when given before exposure. The synthesis also notes that some existing antiviral medicines used to treat orthopox virus infection may be used alone or in combination with vaccines to treat mpox. These include tecovirimat and brincidoforvir, which have been used in the U.K. to reduce viral titres in patients with monkeypox (clade not specified). In addition, the synthesis highlights the importance of personal protective equipment, including masks, goggles, gloves, or specific impervious long-sleeved gowns in clinical settings.(2)

Diagnosis

The same high-quality evidence synthesis noted a lack of monkeypox virus–specific rapid diagnostic kits to support rapid diagnosis.(2) However, a recent single study notes that researchers validated a new real-time PCR assay (dD14-16) that can successfully detect suspected mpox cases of clade Ib.(4)

Diagnostic challenges persist, especially in low-resource settings. Clinicians' diagnosis based on lesion presentation has shown moderate accuracy but poor reliability in distinguishing clade I mpox from varicella (chickenpox). This emphasizes the need for improved diagnostic resources and training in low-resource settings.(14)

Clinical presentation

The recent high-quality evidence synthesis highlighted above also described the clinical presentation of mpox as including a prodromal period with fever, headache, night sweats, myalgia, coryzal illness, and peripheral lymphadenopathy, and after one to two days, the presentation of lesions in the mucosal surfaces and skin.(2)

According to findings presented at a recent international conference convened on 29 and 30 August 2024 by the World Health Organization entitled Aligning Mpox Research Response with Outbreak Goals,(13) the face is the primary rash site in 82% of cases, often with a centrifugal distribution and over 100 lesions in 51% of cases. High rates of lymphadenopathy (80%, mainly submaxillary and cervical) and febrile prodrome (80%) are common.

In contrast, Clade Ib mpox, based on emerging evidence from 2023–2024, shows different characteristics. The clinical presentation of clade Ib often involves primary lesions appearing orally (40%) or genitally (60–85%). Lymphadenopathy was reported in 42% of cases (site unspecified) and 60% experienced fever.

Prognosis

A recent medium-quality evidence synthesis (literature last searched in 2022) found historical data suggested clade I had a higher case fatality rate than clade II at approximately 9.8%, as opposed to 3.5% and 0.1% for clades IIa and IIb.(15) This finding of higher case fatality rates was supported in two single studies reporting case fatality rates of between 7.5% and 11%.(1; 12) However, recent data from the WHO conference presentation mentioned above describes lower mortality rates of between 5–10% for clade Ia, 0.7% for clade Ib, 0% for clade IIa, and 3–5% for clade IIb.(13)

A recent high-quality evidence synthesis (2) noted that there is higher mortality among children, young adults, and those who are immunocompromised, but no mortality rates were reported. One medium quality evidence synthesis reporting on historic data (between 1970 and 2014) noted that the median age for mpox infection in the DRC was under 16.(15) A single study of clade I infections (from 2001 until 2021) in the Central African Republic similarly found particularly high rates of case fatality among children and those in close contact with wildlife.(12)

Treatment

A recent high-quality evidence synthesis (literature last searched in 2023) did not identify any completed randomized controlled trials investigating the effectiveness of therapeutics for treating mpox, but the synthesis identified five ongoing trials that plan to assess the effectiveness of tecovirimat, including on adults, children, and populations with or at greater risk of severe disease.(16) The synthesis noted that findings from non-randomized studies examining the safety of different therapeutics for treating mpox found no serious safety signals for using tecovirimat but possible safety problems with the use of bricidofovir, namely elevated levels of alanine transaminase that meet the requirements for drug-induced mild liver injury (reported in two of three participants that were administered the drug).(16) However, this evidence was assigned a critical overall risk of bias due to the inherent biases associated with the study design.(16)

A recent high-quality evidence synthesis produced in 2022 noted that recovery can be supported by antiviral medications such as tecovirimat and bricidofovir, rehydration therapy and nutritional supports.(2)

A recent single study reported on the use of oral tecovirimat (600 mg twice daily) for treating patients with mpox and reported that by day 14 most individuals had been discharged and were confirmed negative using real-time PCR detecting viral DNA from blood samples or lesion swabs. The study reported that the median time from the initiation of treatment until the absence of active lesions was five days.(17)

Next steps based on the identified evidence

These recommended actions address current knowledge gaps and have been synthesized from both reviewed publications and expert opinion. They aim to improve our understanding and management of clade I mpox outbreaks. A notable cross-cutting suggestion from the literature is the need for future studies to address potential biases and consider a broader range of factors that may influence disease outcomes across different populations. Additionally, researchers should strive to conduct more standardized studies across various settings to facilitate more robust comparisons.

- Supporting the early detection and response to clade I outbreaks, including using standardized reporting protocols, leveraging genomic surveillance to track the evolution of the virus, and strengthened surveillance systems for clade I outbreaks, particularly given the evolving transmission patters and geographic distribution.
  - Leveraging genomic surveillance to track the evolution of the virus.
  - Implementing more active epidemiologic surveillance to better understand the true incidence of mpox.
- Additional research to address key evidence gaps that could inform more effective prevention and control strategies is likely important for the following priority areas:
  - conducting randomized controlled trials on potential treatments specific to clade I mpox
  - evaluating the effectiveness of existing smallpox vaccines against clade I
    - vaccine effectiveness against clade I for various outcomes (infection, disease, severity, mortality)
    - vaccine effectiveness in different subgroups (e.g., age groups, pregnant individuals, immunocompromised populations)
    - vaccine effectiveness for various vaccination strategies (e.g., general population, ring vaccination, post-exposure)
    - duration of protection and correlates of immunity
  - investigating the long-term health outcomes for survivors of clade I infections
  - studying the socio-economic impacts of clade I outbreaks on affected communities
  - examining how environmental factors that influence clade I transmission and persistence
    - adopt a One Health approach to investigate zoonotic transmission
    - evaluate virus survival in various environmental conditions (temperature, humidity, surfaces)
    - investigate the role of fomites in transmission
  - determining the differential effects of clade I mpox on sub-populations
    - examine variations in virulence across different demographic groups

- identify potential confounders and effect modifiers for disease severity and outcomes
- investigate interaction terms between host factors and viral characteristics
- study genetic susceptibility or resistance factors in different populations.

Wu N, Waddell K, Bhuiya A, Bain T, Demaio P, Grewal E, Ali A, Alam S, Loeb M, Wilson MG. Living evidence profile 6.12: Best-available evidence related to the mpox outbreak. Hamilton: McMaster Health Forum, 30 August 2024.

This rapid evidence profile was funded by the Public Health Agency of Canada. The McMaster Health Forum receives both financial and in-kind support from McMaster University. The views expressed in the rapid evidence profile are the views of the authors and should not be taken to represent the views of the Public Health Agency of Canada or McMaster University.

References

1. Pesonel E, Hoffmann I, Guiraud L, et al. MOSAIC: A cohort study of human mpox virus disease. Wellcome Open Res 2023; 8(415).
2. Anjorin A-AA, Odetokun IA, Ashaka OS, et al. Critical appraisal of mpox (Monkeypox) in Africa using scoping and systematic reviews: Epidemiology, Biochemistry, phylogeny, pathogenesis, clinical features, diagnosis, treatment, biosecurity and one-health. Durham, N.C.: Research Square; 2023.
3. Masirika LM, Kumar A, Dutt M, et al. Complete genome sequencing, annotation, and mutational profiling of the novel clade I human mpox virus, Kamituga strain. *J Infect Dev Ctries* 2024; 18(4): 600-608.
4. Schuele L, Masirika LM, Udahemuka JC, et al. Real-time PCR assay to detect the novel Clade Ib monkeypox virus, September 2023 to May 2024. *Eurosurveillance* 2024; 29(32): 2400486.
5. Kinganda-Lusamaki E, Amuri-Aziza A, Fernandez N, et al. Clade I monkeypox virus genomic diversity in the Democratic Republic of the Congo, 2018–2024: Predominance of zoonotic transmission. *medRxiv* 2024: 2024.08.13.24311951.
6. Ponce L, Linton NM, Toh WH, et al. Incubation period and serial interval of mpox in 2022 global outbreak compared with historical estimates. *Emerging Infectious Diseases* 2024; 30(6): 1173.
7. Garba-Ouangole S, Bourner J, Mbrenga F, et al. Laboratory diagnosis of mpox, Central African Republic, 2016–2022. *Emerging Infectious Diseases* 2023; 29(9): 1846.
8. Djuicy DD, Sadeuh-Mba SA, Bilounga CN, et al. Concurrent clade I and clade II monkeypox virus circulation, Cameroon, 1979–2022. *Emerging Infectious Diseases* 2024; 30(3): 432.
9. Sun Y-Q, Chen J-J, Liu M-C, et al. Mapping global zoonotic niche and interregional transmission risk of monkeypox: A retrospective observational study. *SSRN – Lancet prepublication* 2022.
10. Doshi RH, Alfonso VH, Morier D, et al. Monkeypox rash severity and animal exposures in the Democratic Republic of the Congo. *Ecohealth* 2020; 17: 64-73.
11. Kibungu EM, Vakaniaki EH, Kinganda-Lusamaki E, et al. Clade I–associated mpox cases associated with sexual contact, the Democratic Republic of the Congo. *Emerging Infectious Diseases* 2024; 30(1): 172.
12. Besombes C, Mbrenga F, Schaeffer L, et al. National Monkeypox Surveillance, Central African Republic, 2001–2021. *Emerging Infectious Diseases* 2022; 28(12): 2435.
13. Subissi L. Overview of clinical characteristics of various MPXV clades: Aligning mpox research response with outbreak goals: Scientific conference; 2024.
14. Bourner J, Garcia E, Mbrenga F, et al. Challenges in clinical diagnosis of clade I mpox: Highlighting the need for enhanced diagnostic approaches. *medRxiv* 2024: 2024.03.21.24304658.
15. Sharif N, Sharif N, Alzahrani KJ, et al. Molecular epidemiology, transmission and clinical features of 2022-mpox outbreak: A systematic review. *Health Sci Rep* 2023; 6(10): e1603.
16. Fox T, Gould S, Princy N, Rowland T, Lutje V, Kuehn R. Therapeutics for treating mpox in humans. *Cochrane Database Syst Rev* 2023; 3(3): CD015769.
17. Mbrenga F, Nakouné E, Malaka C, et al. Tecovirimat for monkeypox in Central African Republic under expanded access. *N Engl J Med* 2022; 387(24): 2294-2295.