McMaster University | Health Forum

Living evidence profile

Best-available evidence related to the mpox outbreak

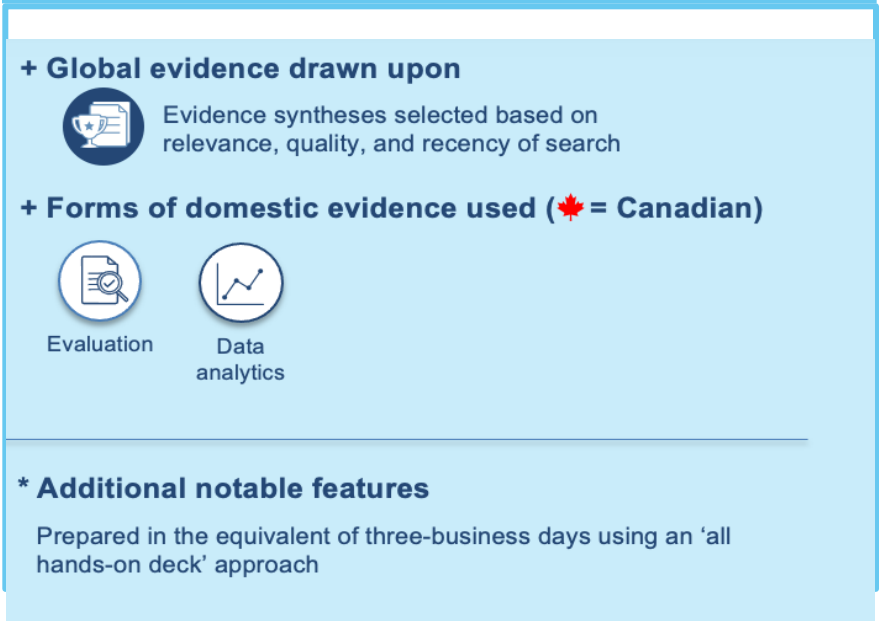
4 December 2024

[MHF product code: LEP 6.13b]

Context

- On 14 August 2024, the WHO declared mpox a Public Health Emergency of International Concern due to the rapid spread of subclade Ib in the eastern Democratic Republic of the Congo (DRC) and five 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).
- Version 12 was published in August 2024, which was requested to solely focus on published evidence syntheses and single studies about clade I (including Ia and Ib) given the global spread.
- To bridge the previous versions from 2022 with the latest developments related to the mpox outbreak in 2024, we identified evidence syntheses related to mpox published between 2019 to 5 November 2024 and any new single studies on clade I (including Ia and Ib) that were published since version 12.
- After removing any duplicate evidence documents, we included a total of 172 evidence documents (evidence syntheses and single studies focused on clade I), which includes 22 identified from version 12 and 150 newly identified documents.
- Given the volume of available research evidence, this update summarizes only the key findings from high-quality evidence syntheses across all clades and newly identified single studies that specifically focus on clade I (Ia and Ib).

Box 1: Evidence and other types of information



Question

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

High-level summary of key findings

- This LEP includes evidence documents from the previous version, giving a total count of 172 evidence documents (140 evidence syntheses, 31 single studies, and one set slides from a global conference).

- We appraised the quality of each evidence synthesis using the AMSTAR tool, categorizing 24 as high-quality, 75 as medium-quality, and 41 as low-quality.
- Our findings focus on new insights from 24 high-quality evidence syntheses related to mpox.
- We also summarize the key findings from seven new single studies focused on clade Ia and/or Ib that we identified since the publication of version 12 in August 2024.
- Most of the evidence documents did not specify the clades or subclades; however, we report them where specified by the evidence.
- Genomic studies provided insights into the recent evolution and spread of mpox, including the circulation of subclade Ia and Ib in Central Africa.
- Subclade Ib appears to have a longer incubation period and slower transmission dynamics than subclade IIb.
- Transmission patterns have shifted from pre- to post-2022, where there has been an increase in human-to-human transmission since 2022.
- Most of the reported mpox global outbreaks have primarily affected men who have sex with men (MSM) and there are growing concerns on the impact of mpox on people living with HIV, women, pregnant people, and children.
- The use of vaccines was predominately described in the available research evidence for the prevention and control of mpox.
- Symptoms of mpox have become more varied over time, although the prevalence of lesions and rashes remains consistent.
- We identified limited evidence about the diagnosis, prognosis, and treatment of mpox; however, there are randomized controlled trials on underway in Canada and the United Kingdom on the effectiveness and safety of tecovirimat.

Box 1: Approach and supporting materials

At the beginning of each living evidence profile and throughout its development, we engage a subject matter expert and citizen partners, who help 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. Updated searches were conducted on 4 September 2024, 1 October 2024, and 5 November 2024 to identify any evidence syntheses about mpox, as well as any single studies focused on clade I since the last version. 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 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.

Note that the timing, frequency, and scope of future updates of this LEP will be determined in collaboration with the requestor.

A separate appendix document includes:
1) methodological details (Appendix 1)
2) overview of the included evidence syntheses and single studies (Appendix 2a-c)
3) Key findings from the high-quality evidence syntheses and new single studies (Appendix 3)
4) details about each identified high-quality synthesis (Appendix 4)
5) details about each identified single study (Appendix 5)
6) categorization of the medium and low-quality syntheses (Appendices 6, 7)
7) documents that were excluded in the final stages of review (Appendix 8)

This update to the living evidence profile was prepared in the equivalent of three day of a ‘full court press’ by all involved staff.

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 a total of 140 evidence syntheses on mpox that were published between 2019 to 5 November 2024. We appraised the quality of each evidence synthesis (using the AMSTAR tool), categorizing 24 as high-quality, 75 as medium-quality, and 41 as low-quality. Additionally, since version 12 published in August 2024, we identified seven new single studies specifically focused on clade I (including Ia and Ib). This LEP also includes evidence documents from the previous version, giving a total count of 172 evidence documents (140 evidence syntheses, 31 single studies, and one slide deck from a global conference).(1-172)

Given the volume of available evidence, we incorporate new insights from the 24 high-quality evidence syntheses across all clades and the seven single studies that were newly identified on clade I to the key findings from the previous version. Details of each identified high-quality evidence synthesis and single study are available in Appendices 4 and 5.

The high-level categorization of the medium and low-quality evidence syntheses are in Appendices 6a and 6b (and the full categorization available in Appendix 7).

Coverage by and gaps in existing evidence syntheses and domestic evidence

The identified high-quality evidence syntheses and single studies provide both historical and current insights of mpox in terms of its biology, epidemiology, high-risk populations, prevention and control, diagnosis, clinical presentation, prognosis, and treatment. Most of the evidence documents did not specify the clades or subclades; however, we report them where specified by the evidence. There appears to be emerging insights on genomics and transmission about subclades Ia and Ib in recent single studies. Further, there are additional studies about high-risk populations such as people living with HIV, women, and children. We also reported on any relevant information to Canada, such as the upcoming randomized controlled trial (PLATINUM-CAN) in Canada to assess the effectiveness and safety of tecovirimat.

There are still gaps in the evidence on mpox. We identified limited information about prevention and control, diagnosis, prognosis, and treatment that differentiated the impacts based on clades and subclades. There continues to be a lack of evidence on the long-term health impacts of mpox infections and the socio-economic consequences of outbreaks in affected communities.

Key findings from included high-quality evidence syntheses and single studies

Biology

Emerging research has highlighted the recent gaps in understanding the biology of mpox and its subclades. A scoping review (pre-print) focusing on clades I and II identified a lack of knowledge related to how the virus alters the host's physiology and biochemistry.(8)

Clade I
Clade I monkeypox virus, historically prevalent in Central Africa, exhibits distinct biological characteristics that set it apart from other clades.(124) 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). This may contribute to its potential for increased virulence, however there is still uncertainty.(8)

A new 2024 global analysis of 10,670 sequences collected from 65 countries (including Canada) revealed that most of the genetic data originated from outbreaks between 2022 and 2024.(121) The study found clade I continues to circulate mainly in Central Africa.

Biologically, the incubation period of mpox can vary between clades. Some studies suggest that clade I may have a longer incubation period compared to other clades, however the current evidence is not clear.(124) However, 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% CI: 7.0–9.2 days) across all clades. Clade I infections were characterized by a mean of 7.3 days (95% CI: 5.0–10.2 days), whereas clade II infections showed a mean of 8.9 days (95% CI: 6.6–11.7 days). However, these differences were not statistically clear and could be due to sampling variability.(128)

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.(51) This genetic analysis capability enhances our understanding of the virus's biology.

Epidemiology

Unspecified clade
The identified evidence syntheses and single studies describe transmission patterns and potential reservoirs for mpox. An evidence synthesis (including three Canadian studies) reported a shift in mpox transmission patterns from pre- to post-2022.(59) The authors reported that prior to 2022, most of the reported cases were caused by animal-to-human transmission, but almost all reported cases since 2022 had a history of human contact, particularly sexual transmission. Another evidence synthesis reported that the 2022 mpox outbreak also saw higher average ages and comorbidity rates than previous years, emphasizing the need for global cooperation to address the spread and impact.(40) In terms of reservoirs, two evidence syntheses indicated that skin lesions have high viral loads, which could contribute to high infectivity and drive rapid transmission, especially during direct skin-to-skin contact through close physical proximity.(132;133)

Clade I
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.(155) The geographic spread of clade I appears to be expanding, with travel-related infections originating largely in Ghana, Côte d'Ivoire, the Democratic Republic of the Congo, and spreading to other countries. Historically, clade I transmission has been primarily zoonotic, with high exposure to rodents (91%) and non-human primates (77%).(36;37) However, recent evidence indicates evolving transmission patterns.(74) A cluster of clade I mpox infections in March 2023 in the Democratic Republic of the Congo was reported to be transmitted through sexual contact, a route previously associated only with clade II.(74)

Subclade Ia and Ib
Genomic studies provided insights into the recent evolution and spread of mpox clades Ia and Ib. Regarding subclade Ia, a study reported that multiple strains of mpox have circulated in the Republic of the Congo during the 2024 outbreak after analysing samples collected from Brazzaville, Point-Noire, Likouala, Cuvette-Centrale, and Plateaux, which were likely introduced through both cross-border human-to-human transmission and direct zoonotic events. The study also indicated that there is evidence of local spread in previously unaffected areas.(171)

For subclade Ib, three new studies from the Democratic Republic of the Congo added insights to understanding transmission modes and disease severity. For example,, clade Ib been linked to sustained human-to--human transmission, including but not limited to sexual transmission.(19;76;162) One of the studies also reported that in addition to subclade Ib being present in the Democratic Republic of the Congo, there appears to be patterns associated with subclade Ia, which suggests multiple zoonotic introductions.(76) These new findings align with studies previously reported (142;152) and with a newly published evidence synthesis on human-to-human transmission patterns.(59)

Clade II
A global genomic analysis reported that clade IIb appears to have shown more cases of human-to-human transmission across different geographical regions spread than clade I.(121) Clade IIb may have faster transmission dynamics compared to clade I and subclade Ib.(104)

High-risk populations

Unspecified clade
Since 2022, most of the mpox outbreaks have primarily affected MSM.(4;59;95) There have also been reported and confirmed cases of mpox among people living with HIV, women, and children. Growing concerns have emerged regarding the impact of mpox among women and children in endemic regions.(140) In pregnant people, moderate to severe monkeypox virus infections have been associated with high rates of miscarriage, intrauterine fetal death, and perinatal loss, highlighting the need for maternal and fetal monitoring according to the seven reported cases in the

synthesis.(28) Among the cases, two were reported to have suspected vertical transmission where one of the fetuses showed hydrops (i.e., severe swelling in the body). However, the authors indicated that the risk of congenital mpox has not been established. As reported in the previous living evidence profile, outbreaks in Central African Republic have occurred since 2018, which primarily affected forested regions and younger populations, with children under 16 being particularly vulnerable.(16) Similarly, in the Democratic Republic of the Congo, 60% of cases were found in children under 14 years of age.(37)

Subclade Ia and Ib
Subclade Ia appears to primarily affect children under the age of 15, who make up more than 90% of cases.(152) Specific to the subclade Ib findings in the Democratic Republic of the Congo, most cases appear to be mainly in adults (85%). Of these cases, 52% are female, and 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, nor is the number of people with viral suppression from treatment as compared to no treatment.(152)

Prevention and control

Unspecified clade
The use of vaccines was predominately described in the available research evidence for the prevention and control of mpox. An evidence synthesis described that the Another evidence synthesis reported that there is limited evidence on the effectiveness of contact-tracing, sexual behaviour modification and asymptomatic testing to prevent the transmission of mpox.(123) For example, the utility of asymptomatic testing was limited, however there may be some utility to raise awareness and increase case finding during an outbreak.An evidence synthesis (literature last searched in 2022) noted the use of smallpox vaccine (MVA-BN vaccine), vaccinia immunoglobulin, and antiviral medicines can be used to prevent spreading of mpox (all clades).(8) 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 mpox (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.(8)

There are variations in vaccine acceptance across different regions of the world. An evidence synthesis reported higher prevalence of mpox vaccination acceptance in Asian and African countries compared to North America and Europe among healthcare workers.(108) Another evidence synthesis reported a higher acceptance in European countries compared to Asian countries. The sub-analysis of the study revealed that vaccine acceptance was highest among the LGBTI communities, followed by healthcare workers and the general population.(161)

Clade II
A 2024 systematic review reported that the MVA-BN vaccine is highly effective in preventing mpox clade IIb, with vaccine effectiveness (VE) estimated at 76% for one dose (95% CI: 64-88%) from 12 studies, and 82% (95% CI:72-92%) for two doses from six studies. Additionally, the vaccine prevented hospitalization with an effectiveness of 67% (95% CI: 55-78%), Post-exposure prophylaxis (PEP) shows limited effectiveness at 20% (95% CI: 24-65%) from seven studies, which was influenced by timing and exposure conditions.(126)

Diagnosis

There appear to be efforts to improve the diagnosis of mpox, including the development and availability of diagnostic kits. Historically, a scoping review from 2022 (pre-print) found that there was a lack of mpox virus-specific rapid diagnostic kits, but rather the available kits at that time were adapted from other viruses such as smallpox or other orthopox viruses.(8) Since then, , a recent 2024 survey indicated that European Centres in the European Union have

showed a high capability for confirming cases by PCR and to identify clades and/or subclades.(82). Further, a previously reported single study noted that researchers validated a new real-time PCR assay (14-16) that can successfully detect suspected mpox cases of clade Ib.(142)

Clinical presentation

Unspecified clade
Symptoms of mpox have become more varied over time between 1970 to 2023, although the prevalence of lesions and rashes remain consistent.(151) According to the findings presented at an international conference convened on 29 and 30 August 2024 by the World Health Organization,(152) 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. Further, an evidence synthesis reported that oral lesions were found to be among the first clinical signs of mpox, and ulcers on the dorsal surface of the tongue and lips were the most commonly affected areas.(12) Another evidence synthesis described the clinical presentation of mpox as including a prodromal period with fever, headache, night sweats, myalgia, coryzal illness (i.e., common cold), and peripheral lymphadenopathy, and after one to two days, the presentation of lesions in the mucosal surfaces and skin.(8)

Two evidence syntheses reported that the mpox virus can lead to eye-related symptoms and complications such as conjunctivitis, eyelid lesions, and in some severe cases, corneal opacity that can cause blindness. These symptoms were found to be more common in Africa compared to other regions, highlighting the need for healthcare workers in endemic regions to prioritize early detection and treatment.(49;136) Other reported symptoms in both clades include otolaryngologic (i.e., headache, sore throat, cough, cervical lymphadenopathy) and neurological and psychiatric presentations (i.e., encephalitis, confusion, seizures) symptoms.(11;143)

Prognosis

Historically, an evidence synthesis reported that the 2022 mpox outbreak was spreading quickly with 35% of cases resulting in hospitalization and 5% fatality rate of both clades.(15) Recent surveillance data from a WHO conference presentation describes global mortality rates between 5–10% for clade Ia, 0.7% for clade Ib, 0% for clade IIa, and 3–5% for clade IIb.(152)

Clade I
Related to high-risk populations, an evidence synthesis reported that pediatric case fatality rate reached 11% (95% CI 4–20) according to a pooled analysis of studies spanning from 1972 to 2023 in 16 countries. Higher fatality rates were observed in clade I compared to clade IIa and IIb in endemic regions.(137) 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.(16)

Treatment

In the context of mpox, an evidence synthesis with 18 uncontrolled studies reported that individuals were treated with tecovirimat (n= 61), cidofovir (n= 7), and brincidofovir (n= 3), where 83% individuals reported to have complete resolution of symptoms. (145) A randomized, placebo-controlled clinical trial (RCT) called PLATINUM-CAN is being conducted in Canada to assess tecovirimat in MPXV infection. It is a sister study to the PLATINUM-UK at Oxford University, where they aim to combine the results of both clinical trials.

A Cochrane review of therapeutics for treating mpox found no evidence from RCTs regarding the efficacy and safety of treatments. However, tecovirimat appears to not cause serious safety concerns (based on very low-certainty evidence), while brincidofovir may cause liver injury.(47) 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.(8) 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.(107)

Next steps based on the identified evidence

We identified several knowledge gaps that were highlighted in the evidence that we included in this rapid evidence profile that could be explored to improve our understanding and management of mpox outbreaks. Generally, there needs to be a focus on generating high-quality evidence syntheses and studies that specify and study the impact of the clades and subclades, particularly on the biology, impact on high-risk populations, prevention and control strategies such as information, education and non-pharmaceutical measures, and prognosis for both general and high-risk populations.

- Continue supporting the early detection of and timely response to outbreaks (clade I and clade II), including using standardized reporting protocols, leveraging genomic surveillance to track the evolution and transmission dynamics of the virus, and strengthen surveillance systems
  - Continue to leverage genomic surveillance to track the evolution of the virus.
  - Implement more active epidemiologic surveillance to better understand the true incidence of mpox.
- Generate evidence related to potential treatments (e.g., randomized controlled trials), investigating the long-term health outcomes for survivors of mpox infections, studying the socio-economic impacts of mpox outbreaks on affected communities, examining how environmental factors that influence mpox transmission and persistence (e.g., describing a One Health approach, virus survival on environmental conditions, investigating the roles of fomites or through air transmission), and exploring effective non-pharmaceutical measures and education (including the use of behavioural science)
- Determine any differentiating diagnosis and prognosis of the mpox clades and subclades

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Citizen partner acknowledgement: We are thankful to our citizen partners Annie-Danielle Grenier and Marion Knutson for their contribution to the living evidence profile by providing feedback that was incorporated into the final report.

This living evidence profile was funded by 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 Public Health Agency of Canada or McMaster University. The authors wish to thank staff members who appraised the evidence syntheses: Sivanesanathan T, Gou D, Chen N, Whyte M, Cheng S, Lee J, Beltran R, Khan S, Vanderhorst S, Saleh S, Alkhawaja S