McMaster University | Health Forum

Living Evidence Profile

Best-available evidence related to the mpox outbreak

30 August 2024

[MHF product code: LEP 6.12]

Appendices

Appendix 1: Methodological details

We use a standard protocol for preparing living evidence profiles (LEP) to ensure that our approach to identifying research evidence is as systematic and transparent as possible in the time we were given to prepare the profile.

Identifying research evidence

For this LEP, we searched PubMed, Scopus, Europe PNC, and SSRN for:
1) evidence syntheses
2) protocols for ongoing evidence syntheses
3) published single studies
4) pre-prints and other emerging evidence (e.g., recent data presented at conferences).

We searched PubMed using an open text search for (((Monkeypox[All Fields] OR Monkeypox*[All Fields] OR "Monkey pox"[All Fields] OR MPXV[All Fields] OR Monkeypox[MeSH Terms] OR Monkeypox virus[MeSH Terms] OR "Variole du singe"[All Fields] OR "mpox" [All Fields])) AND ((clade* 1) OR ("clade* I") OR ("I clade"))) OR ("Congo Basin clade" OR ("Central Africa clade") OR ("CA clade")). We searched Scopus using an open text for: (TITLE-ABS-KEY ((Monkeypox OR "Monkey pox" OR "monkey orthodox" OR simianOR "Simian pox" OR "simian orthodox" OR mpv OR "Monkeypox virus" OR "ovariole du singe" OR "mpox" OR "orthodoxvirose simienne" OR "ovariole simienne")) AND ALL (" clade 1")). We searched EuropePMC using an open text search for ((Title:(Monkeypox) OR Title:("Monkey pox") OR Title:("Monkey orthopox") OR Title:(Simianpox) OR Title:("Simian pox") OR Title:("Simian orthopox") OR Title:(MPXV) OR Title:("Variole du singe") OR Title:("orthopoxvirose simienne") OR Title:("Variole simienne") OR Title:("mpox") OR Abstract:(Monkeypox) OR Abstract:("Monkey pox") OR Abstract:("Monkey orthopox") OR Abstract:(Simianpox) OR Abstract:("Simian pox") OR Abstract:("Simian orthopox") OR Abstract:(MPXV) OR Abstract:("Variole du singe") OR Abstract:("orthopoxvirose simienne") OR Abstract:("Variole simienne") OR Abstract:("mpox")) AND (SRC:PPR)) AND ((clade 1) OR ("clade I")). Finally, we searched SSRN using a key word search for "Monkeypox" or "Simianpox." We also pulled evidence documents that specifically addressed clade I from two previously conducted living evidence profiles on mpox, last updated in 2022 (1; 2).

Evidence documents from the systematic searches were uploaded into Covidence (a software to support conducting evidence syntheses), where staff undertook title and abstract screening followed by full-text review. Documents were screened by a single reviewer. Any questions regarding inclusion or exclusion were settled by the lead author. The team uses a dedicated virtual channel to discuss and iteratively refine inclusion/exclusion criteria throughout the process, which provides a running list of considerations that all members can consult during the first stages of assessment. From the systematic searches, we screened 224 evidence syntheses and single studies (including 13 duplicates), of which 132

went to full-text review. There were 108 documents excluded following a full-text review because they did not provide findings directly relevant to clade I, they were descriptive articles that did not contain methods sections, or they were modelling studies. In addition, we hand searched the documents included in the two previous living evidence profiles and included six documents. In total, we included 30 evidence documents including seven evidence syntheses and 23 primary studies.

During this process we include published, pre-print, and grey literature. We do not exclude documents based on the language of a document. However, we are not able to extract key findings from documents that are written in languages other than Chinese, English, French, Portuguese, or Spanish. We provide any documents that do not have content available in these languages in an appendix containing documents excluded at the final stages of reviewing. We excluded documents that did not directly address the research questions and the relevant organizing framework.

Assessing relevance and quality of evidence

We assess the relevance of each included evidence document as being of high, moderate, or low relevance to the question.

Two reviewers independently appraise the methodological quality of evidence syntheses that are deemed to be highly relevant using the first version of the AMSTAR tool. Two reviewers independently appraise each synthesis, and disagreements are resolved by consensus with a third reviewer if needed. AMSTAR rates overall methodological quality on a scale of 0 to 11, where 11/11 represents a review of the highest quality. High-quality evidence syntheses are those with scores of eight or higher out of a possible 11, medium-quality evidence syntheses are those with scores between four and seven, and low-quality evidence syntheses are those with scores less than four. It is important to note that the AMSTAR tool was developed to assess evidence syntheses focused on clinical interventions, so not all criteria apply to those pertaining to health-system arrangements or implementation strategies. Furthermore, we apply the AMSTAR criteria to evidence syntheses addressing all types of questions, not just those addressing questions about effectiveness, and some of these evidence syntheses addressing other types of questions are syntheses of qualitative studies. While AMSTAR does not account for some of the key attributes of syntheses of qualitative studies, such as whether and how citizens and subject-matter experts were involved, researchers' competency, and how reflexivity was approached, it remains the best general quality-assessment tool of which we're aware. Where the denominator is not 11, an aspect of the tool was considered not relevant by the raters. In comparing ratings, it is therefore important to keep both parts of the score (i.e., the numerator and denominator) in mind. For example, an evidence synthesis that scores 8/8 is generally of comparable quality to another scoring 11/11; both ratings are considered 'high scores.' A high score signals that readers of the evidence synthesis can have a high level of confidence in its findings. A low score, on the other hand, does not mean that the evidence synthesis should be discarded, merely that less confidence can be placed in its findings and that it needs to be examined closely to identify its limitations. (Lewin S, Oxman AD, Lavis JN, Fretheim A. SUPPORT Tools for evidence-informed health Policymaking (STP): 8. Deciding how much confidence to place in a systematic review. *Health Research Policy and Systems* 2009; 7 (Suppl1): S8.)

Preparing the profile

Each included document is cited in the reference list at the end of the LEP. For all included guidelines, evidence syntheses, and single studies (when included), we prepare a small number of bullet points that provide a summary of the key findings, which are used to summarize key messages in the text. Protocols and titles/questions have their titles hyperlinked, given that findings are not yet available.

We then draft a summary that highlights the key findings from all highly relevant documents (alongside their date of last search and methodological quality).

Upon completion, the LEP is sent to the subject matter expert for review.

Appendix 2: Overview of identified evidence syntheses and single studies by organizing framework domains

	Total	Biology	Epidemiology	Prevention and control	Diagnosis	Clinical presentation	Prognosis	Treatment
Total	**30**	**23**	**19**	**8**	**8**	**3**	**9**	**2**
Evidence syntheses	**7**	**4**	**5**	**3**	**2**	**1**	**4**	**2**
• High relevance	5	3	4	2	2	1	3	2
• Medium relevance	-	-	-	-	-	-	-	-
• Low relevance	2	1	1	1	-	-	1	-
Single studies	**23**	**19**	**14**	**5**	**6**	**2**	**5**	**1**
• High relevance	9	9	8	2	1	-	3	1
• Medium relevance	9	6	4	2	3	1	1	-
• Low relevance	5	4	2	1	2	1	1	-

Appendix 3: Details about each identified evidence synthesis

Dimension of organizing framework	Declarative title and key findings	Relevance rating	Living status	Quality (AMSTAR)	Last year literature searched	Availability of GRADE profile	Equity considerations

• Biology
• Clade I
• Epidemiology
  ○ Geographic spread
• Prevention and control
  ○ Surveillance and reporting
• Diagnosis
• Prognosis (e.g., clinical severity, including morbidity and mortality)
	Clade I, associated with Central Africa (Republic of the Congo, Central African Republic, Democratic Republic of the Congo, Gabon, South Sudan, Cameroon), was reported from the 1970s to 2020, primarily transmitted from animals to humans but also through human-to-human contact, characterized by sporadic cases, outbreaks, and endemic occurrences, with a case fatality rate of 9.8% and approximately 1,090 confirmed cases plus about 30,000 suspected cases (1)	High	No	4/9	2023	No	None identified

• Biology
  ○ Clade I
  ○ Clade II
• Epidemiology
  ○ Transmissibility
• Prognosis (e.g., clinical severity, including morbidity and mortality)
	Across Central and West Africa, the Democratic Republic of the Congo (DRC) experiences the greatest burden of disease because of clade I, which is consistently higher than clade II, and children <10 years old predominantly take on the burden of disease (2)	High	No	5/11	Aug 2018	No	Personal characteristics associated with discrimination (e.g. age, disability)

• Treatment	While this Cochrane review of therapeutics for treating monkeypox (mpox) in humans did not identify any evidence from randomized controlled trials (RCTs) about the efficacy and safety of therapeutics for mpox, very low-certainty evidence reported no serious safety signals from the use of tecovirimat for people with mpox infection; however, there was a safety signal raised from very low-certainty evidence that brincidofovir may cause liver injury (3) • In the three included non-randomized studies that assessed safety of mpox treatment (355 received tecovirimat, three received brincidofovir), all of the participants who received brincidofovir reported an increase in the liver enzyme alanine transaminase (ALT), which led to their treatment being discontinued	High	No	9/10	January 2023	No	None identified

• Biology
  ○ Clade I
  ○ Clade II
• Epidemiology
	A recent scoping review identified that there is currently a lack of understanding on how the virus alters the host physiology and/or biochemistry, a lack of mpox virus–specific rapid diagnostic kit, a limited number of national and/or international	High	No	9/10	May 2022	No	None identified

Dimension of organizing framework	Declarative title and key findings	Relevance rating	Living status	Quality (AMSTAR)	Last year literature searched	Availability of GRADE profile	Equity considerations
○ Transmissibility • Prevention and control ○ Non-pharmaceutical measures to prevent infection ○ Non-pharmaceutical measures to control the spread of infections • Diagnosis • Clinical presentation ○ Symptom onset and duration • Prognosis (e.g., clinical severity, including morbidity and mortality) • Treatment	frameworks and policies for controlling mpox, and a limited information on the socio-ecological, economic, and psychological consequences of this disease (4) • A homolog of the vaccinia virus complement control is present in the Congo Basin clade (clade I) and is absent in the West African clade (clade II), which may contribute to the reduced virulence of the latter • Most studies reported humans and animals as the host of mpox, while the authors noted that there are additional reservoirs for mpox infections such as monkeys, Gambian pouched rats, squirrels, elephant shrews, gazelle, and pigs • Clade II is the most documented strain in Africa • Transmission occurred from human-animal-environmental interactions, human-to-human, zoonotic, and cross-species • The clinical signs and symptoms of mpox in humans include fever, headache, night sweats, myalgia, coryzal illness, peripheral lymphadenopathy (a defining feature when compared to smallpox), and after one to two days there could be lesions in the mucosal surfaces and skin (specifically in the face, scalp, trunk, and limbs) • Over the course of two to four weeks, the rash may progress from raised lesions to pustules with fevers, chills, enlarged lymph nodes, headaches, and muscle aches, which all normally disappear after two to three weeks • The majority of the human cases in Africa have been mild disease and recover within a few weeks; higher risk of mortality includes children, young adults, and those immunocompromised • Mpox is believed to be self-limiting and recovery can occur without treatment • The authors reported that antiviral medications (e.g., tecovirimat, brincidofovir) may be used in combination with vaccines • Additional measures could include the use of personal protective equipment (especially for clinical settings involving patients with mpox), rehydration therapy and nutritional support can support management therapy for individuals with mpox • The authors identified gaps in research such as the lack of understanding on how the virus alters the host physiology and/or biochemistry, lack of mpox virus-specific rapid diagnostic kit, limited number of national and/or international frameworks and policies for controlling mpox, and lack of data on socio-ecological, economic, and psychological consequences of this disease						
• Epidemiology ○ Transmissibility ○ Geographic spread ○ High-risk populations	There is high transmissibility of both mpox clades, with travel-related infections from clade 1 originating largely in Ghana, Côte d'Ivoire, and the DRC and spread to France and the U.K. (5) • The evidence synthesis brings together data from literature reviews as well as officially released reports to identify all mpox infections reports of both human and non-human sources since 1958	High	No	4/9	2022	No	None identified

Dimension of organizing framework	Declarative title and key findings	Relevance rating	Living status	Quality (AMSTAR)	Last year literature searched	Availability of GRADE profile	Equity considerations
▪ 2SLGBTQI+ ▪ Children	• As of 24 July 2022, the final database included 49,432 human cases from 78 countries in six regions • Laboratory confirmed diagnosis was made in 37.3% of cases and 86.55% of the patients with available baseline information were male, with a majority of confirmed cases occurring in children • Zoonotic transmission had occurred in 41% of cases, followed by community transmission, travel-related infection, probable men who have sex with men (MSM)-related infection, household transmission, animal trade, and hospital-acquired infection • It was determined that the 2022 outbreak was largely linked to clade II, but prior to 2021 genomic sequences that had been identified as part of the data were evenly grouped between the two • The majority of clade I cases are reported from the DRC, Cameroon, Gabon, Sudan, and Central African Republic • Compared to clade II, the effective reproductive number of clade I over the entire study period was statistically significantly higher (0.81 compared to 0.56, p< 0.001) • However, the effective reproductive number of clade II increased during 2010 to 2017 to become comparable to clade I • Predicted high risk areas for MPVX are largely located in Western Africa and the Congo Basin, but several regions in the northern part of South America, the Caribbean states, and Southeast and South Asia are highly suitable for the MPVX occurrence; this finding does not distinguish between the two clades • Travel-related infections from clade 1 originate largely in Ghana, Côte d'Ivoire, and the Democratic Republic of the Congo and spread to France and the U.K.						
• Biology o Clade I o Clade II • Prognosis (e.g., clinical severity, including morbidity and mortality)	Hospitalization rates across studies of clade I, clade II, and unspecified clade monkeypox were approximately 14.3%, but fell to about 5.8% during the 2022 outbreak, while estimated case fatality rate was 0.03% but varied considerably depending on care availability and patient demographics (6) • Higher mortality rates were seen in children under 10 in previous outbreaks, while the 2022 outbreak predominantly affected young men with low mortality rates • HIV-positive individuals had worse outcomes, with higher hospitalization rates and mortality • The included studies included research conducted in Italy, Spain, Nigeria, Portugal, U.K., U.S., Central African Republic, Republic of the Congo, and Sudan, which were subsequently analyzed together	Low	No	7/11	Aug 2022	No	Personal characteristics associated with discrimination (e.g. age, disability)
• Epidemiology o Transmissibility	Surveillance systems for outbreaks such as mpox need to be strengthened given that neglected zoonoses could lead to potential global health threats as seen by	Low	No	1/9	February 2023	No	Not reported

Dimension of organizing framework	Declarative title and key findings	Relevance rating	Living status	Quality (AMSTAR)	Last year literature searched	Availability of GRADE profile	Equity considerations
○ Geographic spread • Prevention and control ○ Surveillance and reporting	the clade II MPXV outbreak with over 86,000 cases in 110 countries during the 2022 global outbreak (7)						

Appendix 4: Details about each identified single study

Dimension of organizing framework	Declarative title and key findings	Relevance rating	Study characteristics	Equity considerations

• Biology
  ○ Clade I
  ▪ Subclade Ib
• Epidemiology
  ○ Geographic spread
• Prevention and control
  ○ Surveillance and reporting
• Diagnosis
• Prognosis (e.g., clinical severity, including morbidity and mortality)
	Clade I monkeypox virus, historically prevalent in Central Africa and associated with higher case fatality rates, has recently evolved to include a novel sub-lineage (clade Ib) in the Democratic Republic of the Congo (8)
	• In 2023–2024, there was a surge in MPXV clade I virus cases in Africa, with over 20,000 cases and 1,000 deaths reported across 25 of 26 provinces in the Democratic Republic of the Congo (DRC) by June 2024
	• A novel monkeypox virus sub-lineage, clade Ib, emerged in South Kivu, DRC, in September 2023, primarily spreading through heterosexual transmission
	• Researchers developed and validated a new real-time PCR assay (dD14-16) that successfully identified 82 out of 92 suspected mpox cases in South Kivu as clade Ib, with whole genome sequencing confirming the results for samples with low Cq (quantification cycle) values (below 30)
		High	Publication date: 2024
			
			Jurisdiction studied: Democratic Republic of the Congo
			
			Methods used: Combination of laboratory techniques, clinical sample testing, and genomic analysis
				None identified

• Biology
  ○ Clade I
• Epidemiology
  ○ Geographic spread
• Prevention and control
  ○ Surveillance and reporting
• Prognosis (e.g., clinical severity, including morbidity and mortality)
	Clade I mpox, primarily circulating in Central Africa, is associated with higher morbidity, a longer incubation period (13 days, range 3–34 days), and a higher case fatality rate (approximately 11%) compared to other clades (9)	High	Publication date: 2023
			
			Jurisdiction studied: European Union, the United Kingdom, Switzerland, and Singapore
			
			Methods used: Multi-centre, multi-country cohort
				None identified

• Biology
  ○ Clade I
  ○ Clade II
• Epidemiology
  ○ Transmissibility
  ○ Geographic spread
  ○ High-risk populations
  ▪ Children
• Prognosis (e.g., clinical severity, including morbidity and mortality)
	Clade II monkeypox was found to have a lower case fatality rate (2.2%), compared to clade I (7–10%) (10)
	• Mpox primarily circulates in southern, forested regions of Cameroon, with no cases reported in dry Sahelian areas, suggesting ecosystems play important roles in transmission
	• Clades I and II circulate concurrently, but are geographically segregated, possibly due to natural barriers like rivers and highlands
		High	Publication date: 2024
			
			Jurisdiction studied: Cameroon
			
			Methods used: Observational study
				Personal characteristics associated with discrimination (e.g. age, disability)

• Biology
  ○ Clade I
• Epidemiology
  ○ Transmissibility
	A cluster of clade I MPXV infections was reported in the DRC that was transmitted through sexual contact, previously only associated with clade II (11)
	• The findings indicate that monkeypox can spread through unrecognized transmission routes, highlighting the importance of screening, including clinical, diagnostic, and surveillance approaches in both endemic and non-endemic regions
		High	Publication date: 2024
			
			Jurisdiction studied: Democratic Republic of the Congo
				None identified

Dimension of organizing framework	Declarative title and key findings	Relevance rating	Study characteristics	Equity considerations
			Methods used: Descriptive study	

• Biology
  ○ Clade I
• Epidemiology
  ○ Transmissibility
  ○ Geographic spread
	Phylogenetic analysis and genome annotation indicate that a novel lineage (termed Subgroup VI) of clade I mpox is driving a cluster of infections with a unique, pathogen-favouring mutational profile (12)
	• The study details the genome annotation, phylogeny, and mutational profile of a novel, sustained clade I mpox outbreak in Kamituga, Eastern DRC
	• Seven proteins (C9L, I4L, L6R, A17L, A25R, A28L, and B21R) have emerged as mutation hotspots with inframe deletions, frameshift variants, synonymous variants, and amino acid substitutions
	• A deletion of the D14L (OPG032) gene was found in all samples
	• The phylogenetic analysis confirms that this cluster of mpox infections is genetically distinct from previously reported clade I outbreaks
	• This clade I outbreak shows unique characteristics, including human-to-human transmission through heterosexual and non-sexual contact (community spread), which are rarely observed in clade I outbreaks
		High	Publication date: 30 April 2024
			
			Jurisdiction studied: Kamituga, South Kivu Province, DRC
			
			Methods used: Prospective, observational cohort study
				None identified

• Treatment	A 14-day course of tecovirimat was used to treat 14 patients with mpox, of which majority identified as female with a median age of 23 years in Central African Republic; most were discharged 14 days after the start of treatment (13) • The study focused on the outcomes of tecovirimat, an antiviral drug to combat orthopoxviruses, including mpox • 14 patients from the Central African Republic tested positive for mpox between December 2021 and February 2022 • The median age was 23 years old, of which majority were female • The median time from symptom onset to the initiation treatment was 21 days • All patients presented muscle pain, lesions (11 people had more than 100 lesions), headache, and lymphadenopathy • All patients received a 14-day oral course of tecovirimat (600mg twice daily) • By day 14, 12 patients had been discharged and were PCR-negative and recovered • The median time from the initiation of treatment until the absence of active lesions was five days	High	Publication date: 30 November 2022 Jurisdiction studied: Central African Republic Methods used: Intervention	Not reported

• Biology
  ○ Clade I
  ○ Clade II
	The study suggests that the positive selection signals represent host adaptation signatures, contributing to the differing virulence levels between clade I and II MPXV (14)
	• Signs of positive selection were detected in genes related to immunomodulation and virulence, suggesting adaptation to host immune systems
	• Some genes showing positive selection are involved in manipulating the host's cellular pathways for sensing cytosolic DNA, while others might indicate antibody escape or immune pressures
		High	Publication date: 20 May 2023
			
			Jurisdiction studied: MPXV genomes belonging to clades I and II were retrieved from the National Center for Biotechnology Information database (data primarily
				None identified

Dimension of organizing framework	Declarative title and key findings	Relevance rating	Study characteristics	Equity considerations
			used from the Democratic Republic of the Congo and Central African Republic) Methods used: Observational	

• Biology
  ○ Clade I
  ▪ Subclade Ia
• Epidemiology
  ○ Transmissibility
  ○ Geographic spread
	Monkeypox clade Ia sequences from the Republic of the Congo (RoC) had close genetic relatedness to sequences from the DRC in early 2024, indicating possible cross-border transmission between the two countries; there was also indication from phylogenetic positioning of RoC sequences that multiple strains are con-circulating in the human population (15)
	• Samples from suspected cases of monkeypox were collected from five regions in RoC between January and 29 April 2024; a total of 31 confirmed cases were included
		High	Publication date: August 2024 (pre-print)
			
			Jurisdiction studied: Republic of the Congo, Democratic Republic from Congo
			
			Methods used: Molecular analysis of blood samples
				None identified

• Biology
  ○ Clade I
  ▪ Subclade Ia
  ▪ Subclade Ib
• Epidemiology
  ○ Geographic spread
	The epidemic in the DRC currently has zoonotic spillover involving clade Ia in traditional endemic regions, in addition to a clade Ib outbreak driven by human-to-human transmission in the eastern part of the country (16)
	• 581 samples were collected from individuals in the DRC, where all newly generated MPXV sequences belonged to clade I
	• Majority of the samples belonged to clade 1a, whereas 17 were from clade Ib strains that came from patients infected in 2024
		High	Publication date: 22 August 2024
			
			Jurisdiction studied: Democratic Republic of the Congo
			
			Methods used: Observational
				None identified

• Biology
  ○ Clade I
• Epidemiology
  ○ Transmissibility
	The monkeypox virus isolated during this 2005 outbreak in Sudan appears to be a novel virus belonging to the Congo Basin clade (17)
	• The hemagglutinin gene (942 bp) of the Sudan viruses was identical to that of the MPXV Congo Basin strain MPXV2003_DRC and MPXV1979_Zaire
	• Human-to-human transmission of monkeypox virus was documented for up to five generations in three chains of transmission, with 14 of 19 case-patients reporting contact with a suspected monkeypox case before onset of symptoms
	• Clade I had 6 nucleotide changes compared to the West African strains
	• The outbreak exhibited a notably low case-fatality rate, with all 19 identified monkeypox cases recovering from the illness and no deaths reported
		Medium	Publication date: 2023
			
			Jurisdiction studied: Unity State, Sudan
			
			Methods used: Retrospective epidemiological investigation cohort
				None identified

• Biology
  ○ Clade I
• Epidemiology
  ○ Geographic spread
• Prevention and control
	A nosocomial outbreak of monkeypox in the Central African Republic in 2015–2016, caused by a Zaire genotype strain of the Congo Basin clade, involved 10 cases and spread through familial, healthcare-related, and transport-related transmission (18)	Medium	Publication date: 2017
			
			Jurisdiction studied: Central African Republic
			
			Methods used: Case series
				None identified

Dimension of organizing framework	Declarative title and key findings	Relevance rating	Study characteristics	Equity considerations
○ Surveillance and reporting				
• Biology ○ Clade I ○ Clade II • Epidemiology ○ Transmissibility ○ Geographic spread	Clade I monkeypox exhibited diverse subpopulations without geographic structuring in the Congo Basin, while clades 2/3 were found to be geographically structured, separated by the Dahomey Gap in West Africa (19)	Medium	Publication date: 2023 Jurisdiction studied: Central and West Africa Methods used: Retrospective analysis of MPXV genomes	None identified
• Biology ○ Clade I ○ Clade II • Epidemiology ○ Transmissibility • Diagnosis	Approximately one-third of suspected monkeypox cases in the Central African Republic were confirmed via PCR testing as MPXV infections, with active lesions and scab specimens providing higher viral loads and better detection rates than blood samples (20)	Medium	Publication date: 2023 Jurisdiction studied: Central African Republic Methods used: Retrospective descriptive study	None identified
• Biology ○ Clade I ○ Clade II • Diagnosis	The MPXV-RCC (combined recombinase polymerase amplification (RPA) with CRISPR/Cas12a-based detection) was found to be rapid and reliable as a diagnostic tool for detecting mpox within one hour, while differentiating between clades and showing no cross-reactivity with other pathogens (21)	Medium	Publication date: 2023 Jurisdiction studied: China (laboratory study) Methods used: Diagnostic tool development	None identified
• Biology ○ Clade I ○ Clade II • Diagnosis	A visual assay panel was developed for detecting MPXV DNA and was found to be a highly specific tool differentiating clades and providing results within 25 minutes (22) • The panel was found to be more sensitive than previous methods while showing no cross-reactivity	Medium	Publication date: 2023 Jurisdiction studied: China (laboratory study) Methods used: Diagnostic tool development	None identified
• Biology ○ Clade I • Epidemiology ○ Transmissibility • Clinical presentation ○ Symptom onset and duration ○ Complications	The majority (67%) of monkeypox cases presented with mild rash, while 33% had more severe presentations most often seen in males (69.5%) and children (60% under 14 years of age) in forested areas (23) • High exposure to rodents (91%) and non-human primates (77%) was common before onset of rash	Medium	Publication date: 2020 Jurisdiction studied: Democratic Republic of the Congo Methods used: Observational study	Personal characteristics associated with discrimination (e.g. age, disability)

Dimension of organizing framework	Declarative title and key findings	Relevance rating	Study characteristics	Equity considerations
• Biology ○ Clade I ▪ Subclade Ia ▪ Subclade Ib ○ Clade II ▪ Subclade IIa ▪ Subclade IIb	The heterogeneity of monkeypox 2022 genomes, including clusters in subclade 1 and subclade 2, may prompt the viruses to frequently acquire, truncate, lose, and delete genes and require continuous surveillance of trends in virulence and transmission (24)	Medium	Publication date: October 2022 Jurisdiction studied: China Methods used: Pre-print of a bioinformatics analysis study	None identified
• Biology ○ Clade I ○ Clade II ▪ Subclade IIb	Monkeypox virus genome was sequenced; sample demonstrated close relationship to clade IIb (25) • DNA purification and sequencing of a sample obtained from vesicular lesions of a male patient • Analysis showed a 98.77% identity to monkeypox virus (MPXV) clade I and a 99.42% identity to MPXV clade IIb	Low	Publication date: 2022 Jurisdiction studied: Colombia Methods used: MPXV genome analysis	None identified
• Prevention and control ○ Non-pharmaceutical measures to prevent infection	The NeuMoDx MPXV assay was tested by multiple European and U.S. sites using 296 clinical samples, which found an overall analytical sensitivity of 50 copies/mL for both clades I and II as well as high sensitivity (99%) and high specificity (96%) for lesion swap samples and can differentiate clades I and II (26)	Medium	Publication date: 2024 Jurisdiction studied: United States, Belgium, Spain Methods used: Sensitivity and reliability of a real-time PCR assay	None identified
• Biology • Epidemiology ○ Transmissibility ○ Geographic spread	The samples collected in Beijing from May to July 2023 were all found to belong to the MPXV C.1 lineage, of which two were identified as imported infections from Thailand (27)	Low	Publication date: 2023 Jurisdiction studied: Beijing, China Methods used: Observational	None identified
• Biology	DNA extracted from a lesion is enough to conduct a complete genome sequencing of MPXV strain, which is enough to understand the origin of the virus with sufficient accuracy (28) • The study evaluated MinION real-time TGS sequencing of a MPXV strain	Low	Publication date: 24 June 2022 Jurisdiction studied: Central African Republic Methods used: Observational	Not reported
• Diagnosis	The use of real-time PCR assays was found to be useful for testing suspected clinical samples of both clades with good levels of accuracy, thus these rapid diagnostic tests may be a useful approach to diagnosing cases of mpox (29)	Low	Publication date: 23 June 2022 Jurisdiction studied: Belgium	None identified

Dimension of organizing framework	Declarative title and key findings	Relevance rating	Study characteristics	Equity considerations
			Methods used: Observational	

• Biology
  ○ Clade I
  ○ Clade II
  ▪ Subclade IIa
  ▪ Subclade IIb
• Epidemiology
  ○ Transmissibility
  ○ Geographic spread
• Prevention and control
  ○ Information and education (e.g., including risk communication)
  ○ Surveillance and reporting
• Diagnosis
• Clinical presentation
  ○ Variability in clinical presentation
• Prognosis (e.g., clinical severity, including morbidity and mortality)
	Clinicians showed moderate accuracy but poor reliability when distinguishing clade I mpox from varicella (chickenpox) based on lesion presentation (e.g., the appearance of skin lesions) and faced challenges in consistently classifying lesion stages, especially when multiple types of lesions were present, highlighting the need for improved diagnostic resources and training in low-resource settings (i.e., areas with limited access to medical facilities and tools) (30)
	• The study focused on evaluating the reliability and agreement among clinicians in diagnosing clade I mpox versus varicella (i.e., differentiating between two diseases) and in classifying lesion stages (e.g., identifying the progression of skin lesions) based on clinical signs and symptoms
	• This involved presenting clinicians with 17 images of clade I mpox and varicella lesions to assess their ability to diagnose and categorize lesion stages
	• The study identified moderate accuracy, poor reliability, and moderate agreement among clinicians when distinguishing between clade I mpox and varicella based on lesion presentation (e.g., visible differences in skin lesions)
		Low	Publication date: 2024
			
			Jurisdiction studied: Democratic Republic of the Congo, Central African Republic, France, Belgium, Switzerland, United Kingdom, and Nigeria
			
			Methods used: An inter-rater reliability and agreement study using a questionnaire
				None identified

Appendix 5: Documents excluded at the final stages of reviewing

Document type	Hyperlinked title
Evidence syntheses	Neurological and psychiatric presentations associated with human monkeypox virus infection: A systematic review and meta-analysis
	The changing epidemiology of human monkeypox—a potential threat? A systematic review
Single studies	Genetic insights into the microevolutionary dynamics and early introductions of human monkeypox virus in Mexico
	Anal monkeypox disease: Description of 65 cases
	Monkeypox outbreak 2022, from a rare disease to global health emergency: Implications for travellers
	Recombinase polymerase amplification assay for rapid detection of Monkeypox virus
	Molecular evolution of 2022 multi-country outbreak-causing monkeypox virus clade IIb
	Real-time PCR assays for the specific detection of monkeypox virus West African and Congo Basin strain DNA
	Epidemiology of the 2022 mpox outbreak in the US Veterans Health Administration
	Phylogenomic analysis of the monkeypox virus (MPXV) 2022 outbreak: Emergence of a novel viral lineage?
	Ongoing mpox outbreak in Kamituga, South Kivu province, associated with monkeypox virus of a novel clade I sub-lineage, Democratic Republic of the Congo, 2024
	U.S. preparedness and response to increasing clade I mpox cases in the Democratic Republic of the Congo – United States, 2024
	Interim clinical Treatment Considerations for Severe Manifestations of mpox – United States, February 2023
	Viral dynamics in patients with monkeypox infection: A prospective cohort study in Spain
	Incubation period, serial interval, generation time and reproduction number of mpox clade I
	Orthopoxvirus-specific antibodies wane to undetectable levels one year after MVA-BN vaccination of at-risk individuals
	Intrafamily transmission of Monkeypox Virus, Central African Republic, 2018
	Maternal and fetal outcomes among pregnant women with human monkeypox infection in the Democratic Republic of Congo
	Modelling human-to-human transmission of monkeypox
	Potential for monkeypox exportation from West and Central Africa through global travel networks
	Tecovirimat for Monkeypox in Central African Republic under expanded access
Descriptions	The global alarm bell is ringing due to the threat of potential severe cases and deaths caused by clade I of monkeypox virus
	Clinical review of human mpox

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