Monkeypox virus Clades & Subclades Overview

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Monkeypox virus (MPXV) emergence and circulation

MPXV Timeline

1958: MPXV identified in captive NHPs

1970: human mpox identified

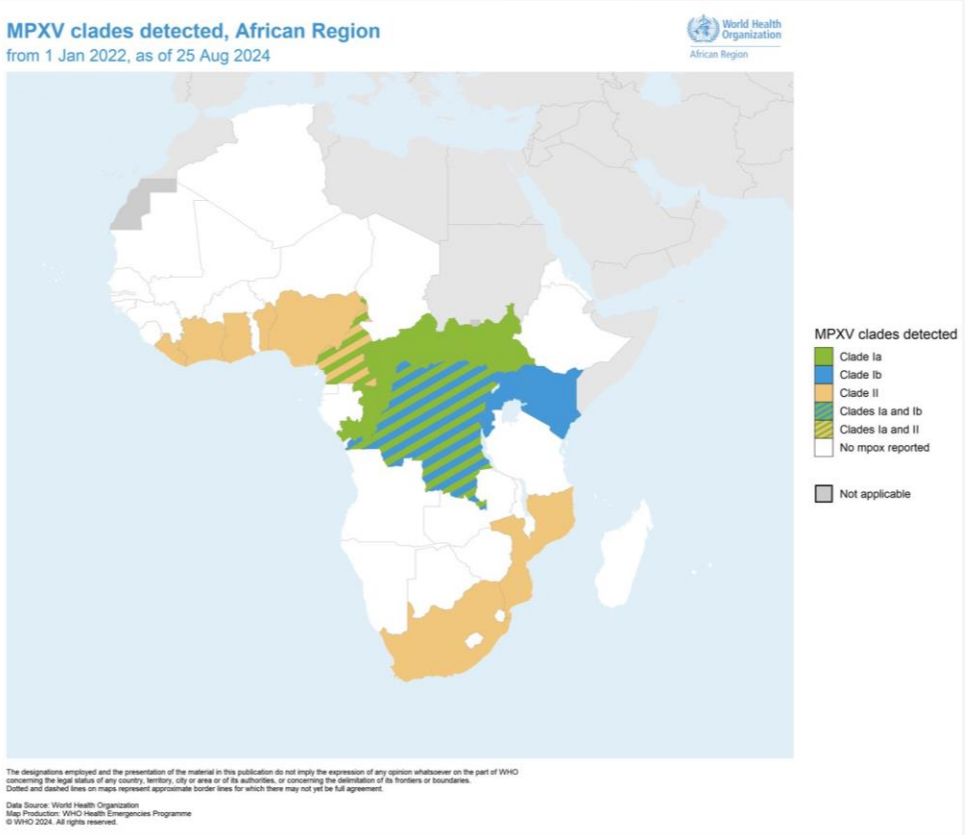
1980: WHO announces global eradication of VARV

-continual increase in MPXV infections in Africa

2003: US outbreak of MPXV clade IIa

2017: re-emergence of MPXV clade IIb in Nigeria

2022: global emergence of MPXV clade IIb



Historical considerations:

Clade I MPXV

- Endemic in Central African regions
- 5-10% case fatality rate

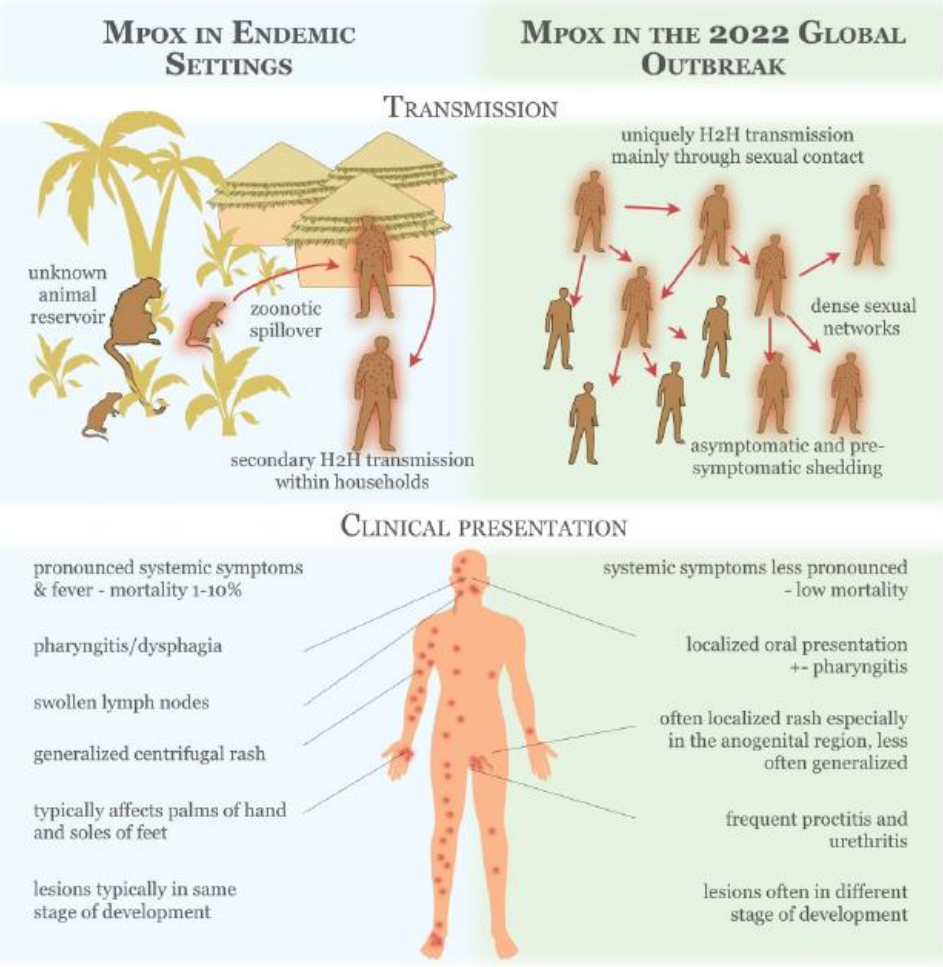
Clade II MPXV

- Endemic in West Africa regions
- Less severe disease

~95% NA sequence homology

Diversity in proteins related to modification of host responses

Epidemiology and clinical features of human mpox



Clade IIa – west of Dahomi Gap

Clade IIb – east of Dahomi Gap in Nigeria

Nucleotide difference b/w clade I and clade IIa genomes is 4–5%; difference between IIa and IIb is ~2%

Table 1
Clinical presentation of human mpox across MPXV clades

Global location	Endemic regions of central and West Africa (from 1970)	Non-endemic regions (from 2022)
Virus clade(s) Regions affected	Clade I and clade II Clade I: DRC, Republic of Congo, Central African Republic, South Sudan, Gabon, Cameroon Clade II: Nigeria, Liberia, Sierra Leone, Côte d'Ivoire, Cameroon	Clade IIb 111 countries across all 6 WHO regions
Primary affected population	Children (<10 y of age) with most deaths between 0 and 4 y for clade I; clade II infections in Nigeria from 2017 to present predominantly in young men (20–40 y of age)	Men who have sex with men (84% of cases with known sexual orientation); median age 34 y (highest among 18–44 y of age); HIV positivity associated with 52% of cases with known HIV status
Primary transmission mechanism	Zoonotic transmission (bites, scratches, lesion contact) with limited human-to-human transmission	No known zoonotic link; exclusively human-to-human transmission
Route of viral dissemination	Predominant household and limited nosocomial transmission	Primarily through sexual close contact (most common exposures in party settings with sexual contacts)
Clinical disease	Prodromal phase (pronounced systemic symptoms with fever) followed by synchronous lesion development with generalized centrifugal rash; cervical or axillary lymphadenopathy; pharyngitis	Less-pronounced prodromal phase; fever; localized vesiculopustular rash with asynchronous lesion development (anogenital most prominent); frequent proctitis and urethritis; localized oral presentation with or without pharyngitis; inguinal lymphadenopathy
Case fatality rates (%)	1–15	0.2

Data reflect the period from 1 January 2022 to 9 May 2023 [32].
DRC, Democratic Republic of the Congo; MPXV, monkeypox virus.

Van Dijke C, et al. *Clin Microbiol Inf.* [Accepted]

Okwor T, Mbala P, Evans D, Kindrachuk J. *Clin Microbiol Inf.* [Accepted]

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Monkeypox virus (MPXV) Lethality

Table 1 | MPXV clades

	MPXV clade I	MPXV clade IIa	MPXV clade IIb	VARV[e]
Endemic	Central Africa[a]	West Africa[b]	West Africa[c]	Eradicated
Global outbreak	No	2003	2018–2023	Eradicated
Animal reservoir	Multiple	Multiple	Multiple	None
Vesicular lesions	Yes	Yes	Yes	Yes
Lethality	10.6%	Low	3.6%[d]	~35%
Select agent	Yes	No	No	Yes
Vaccine[f]	Yes	Yes	Yes	Yes
Therapeutic[g]	Yes	Yes	Yes	Yes

[a]Mainly DRC. [b]Ivory Coast, Liberia, Sierra Leone, Ghana, Cameroon. [c]Nigeria. [d]Deaths in outbreak in Nigeria. [e]Variola virus cause of smallpox. [f]Smallpox vaccines Jynneos and ACAM2000. [g]Tecoviramat, brincidofovir and cidofovir.

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Moxx B. *Nature Micro. 2024. 9: 1408-1416*

Monkeypox virus (MPXV) Lethality

Animal	Virulence (route)	Symptoms	Reference
Cynomolgus macaques	I>IIa (aerosol, s.c.)	Lethal, rash	70,71
Ground squirrel	I~IIa (s.c.)	Lethal	90,91
Prairie dog	I>IIa (i.n., s.c.)	Lethal, rash, transmission	92–94
Deer mouse	I~IIa>IIb (i.n.)	Asymptomatic, PCR+	95
Rope squirrel	I (i.n., s.c.)	Lethal	96
Gambian pouched rat	I (i.d., i.n.)	Clinical, subclinical	97
African dormouse	I~IIa (i.n.)	Lethal	76
Multimammate rat	IIb (mucosal)	Lesions, transmission	77
Mouse (BALB/c, C57BL/6)	I>IIa (i.n.)	Mild weight loss	79
SCID-BALB/c	I>IIa (i.p.)	Lethal	78
Mouse (CAST/EiJ)	I>IIa>IIb (i.n., i.p.)	I and IIa lethal; IIb PCR+ and asymptomatic	44,76,80

s.c., subcutaneous; i.d., intradermal; i.n., intranasal; i.p., intraperitoneal; PCR+, polymerase chain reaction positive.

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Clade IIb re-emergence and MPXV Case Fatality Rates

Table 2. Number of Cases per Clade[1].

Decade	Central African Clade (N)	West African Clade (N)	Total Cases
1970–1979	38	9	47
1980–1989	355	1	356
1990–1999	520	0	520
2000–2009	92 confirmed 10,027 suspected[2]	47	139 10,027
2009–2019	85 confirmed 18,788 suspected[2]	195	280 18,788

[1] The five cases from Cameroon are not included in this table, as clade was not reported in any of the articles and WHO reported that Cameroon is the only country in which both clades have been detected [12].

[2] Suspected cases are from the Democratic Republic of the Congo, as number of suspected cases rather than confirmed cases were primarily reported. Suspected cases for other countries are not reported since testing of suspected cases was generally undertaken.

Table 3. Pooled case fatality rate in confirmed, probable, and/or possible monkeypox cases.

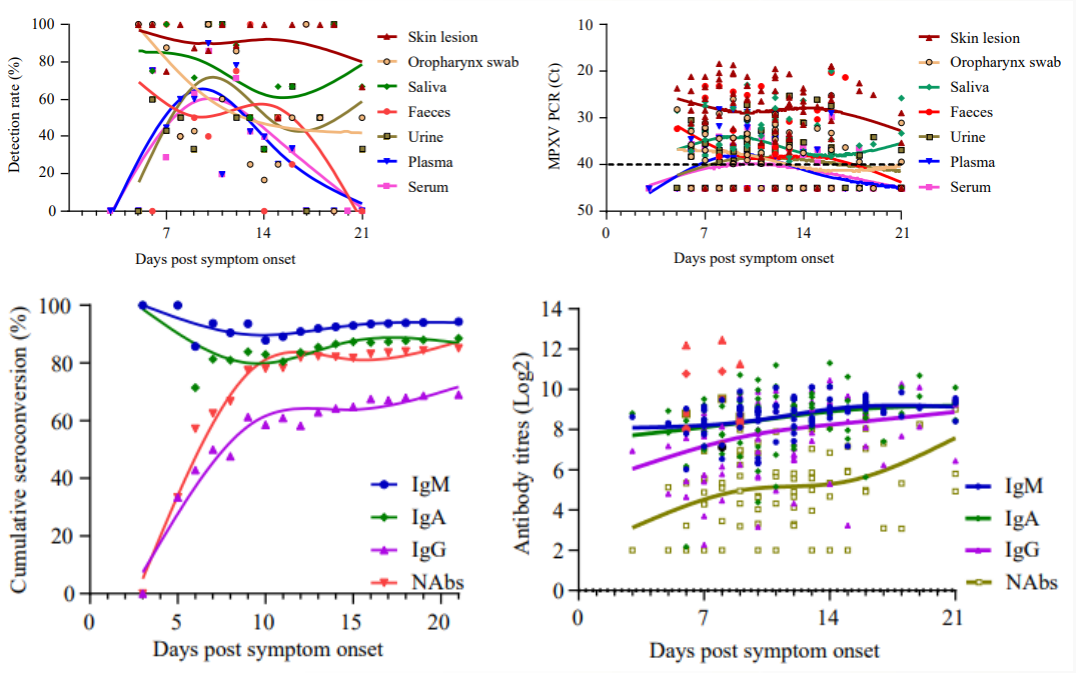
Countries/Clade	Case Fatality Rate	95% CI[1]
All countries[2]	78/892 = 8.7%	7.0%– 10.8%
Central African clade[3]	68/640 = 10.6%	8.4%– 13.3%
West African clade[4]	9/247 = 3.6%	1.7%– 6.8%
West African clade, African countries only	9/195 = 4.6%	2.1%– 8.6%

- significant difference between clades—Central African 10.6% (95% CI: 8.4%– 13.3%) vs. West African 3.6% (95% CI: 1.7%– 6.8%)
- Dominance of Clade I vs Clade II cases for data extrapolation (most Clade II data from US outbreak and 2017 re-emergence in Nigeria)

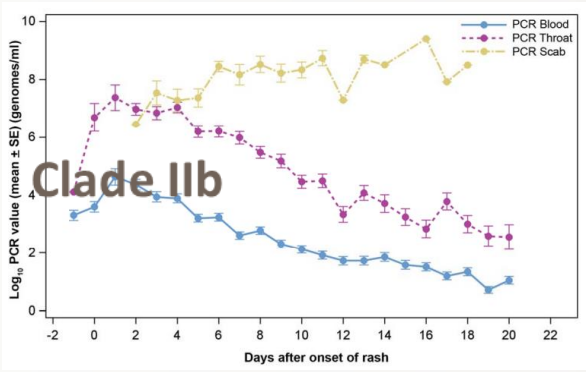
Bunge E et al. *PLOS Negl Trop Dis*. 2022. 16: e0010141

MPXV Virological Insights

Clade IIb

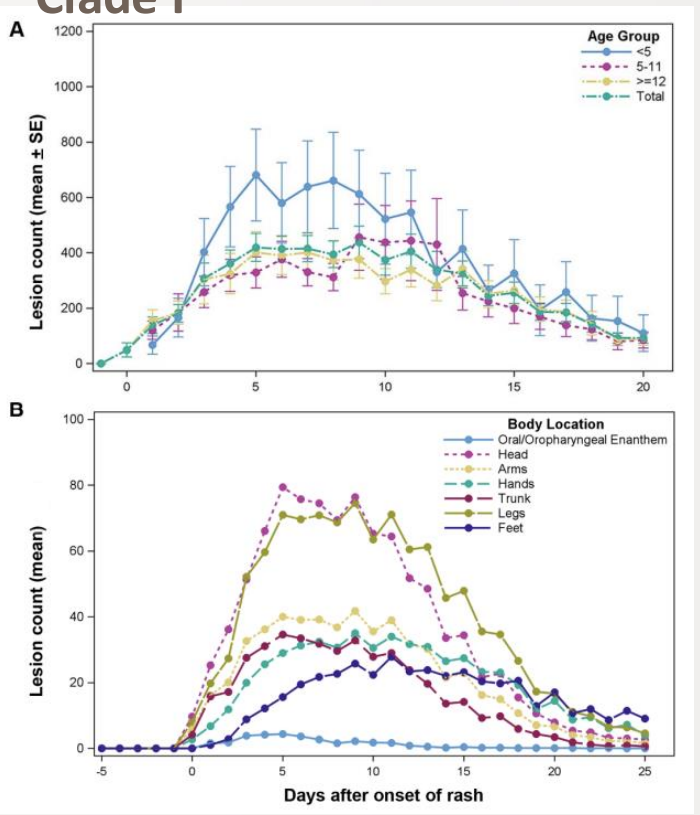


Guo L et al. EBioMedicine. 2024. 106:105254



Pittman PR et al. medRxiv. 2022

Clade I



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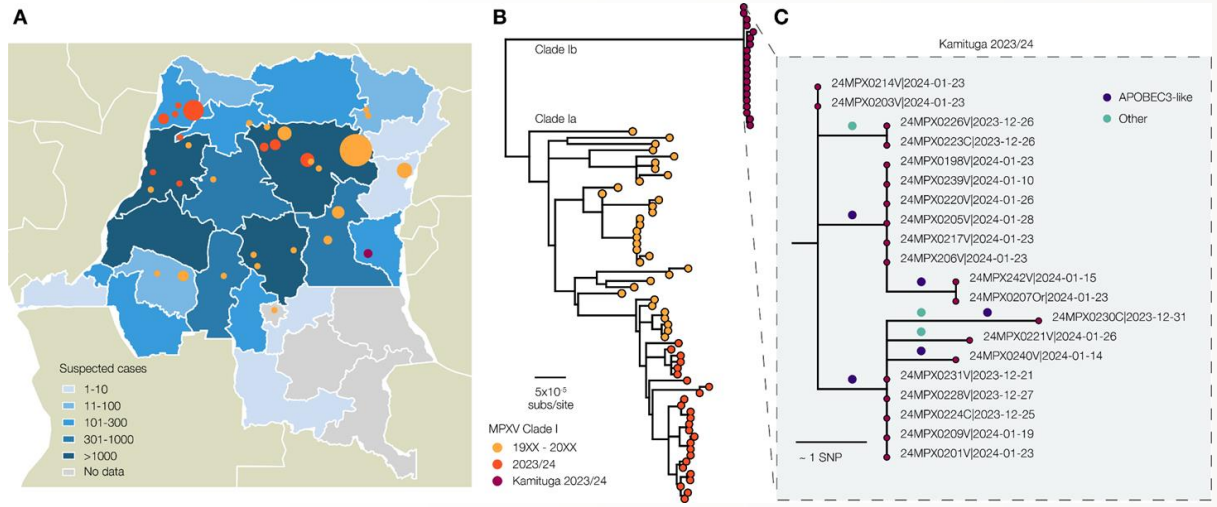
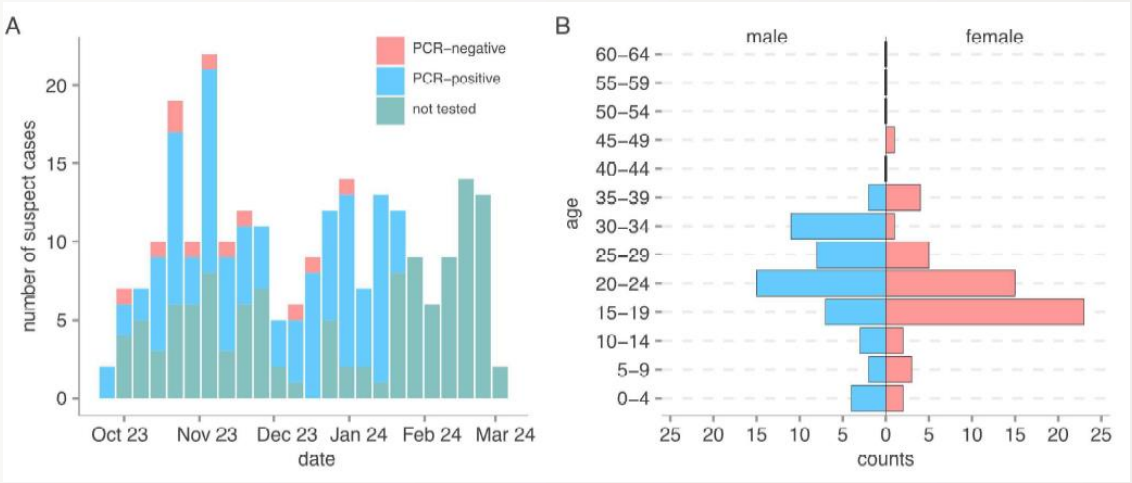
Clade Ib MPXV transmission among sex workers – Kamituga, DRC



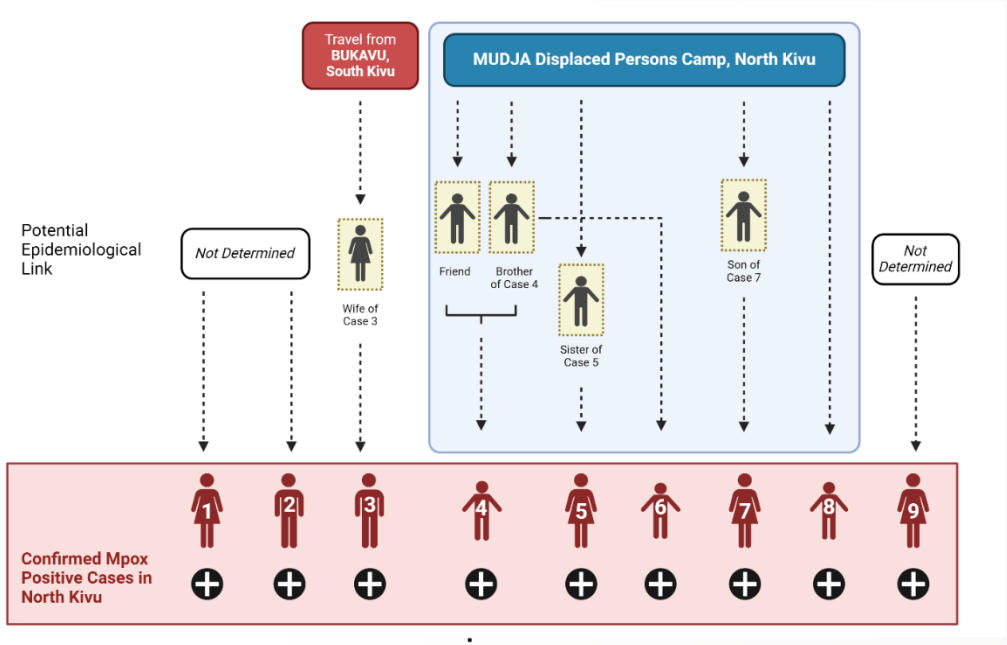


- first identified cases of mpox identified in Kamituga (224/241 susp. cases in S. Kivu Sep 2023 to Feb 2024)
- Mutations identified in APOBEC3 suggestive of inc. h2h transmission
- Recommend designation of new subclade - Clade Ib (prior Clade I to Clade Ia)

- Cases mostly among 15-30 years (67%)
- 52% females
- ~30% among sex workers
- 85% presented w/ genital lesions
- 22/25 interviewees reported contact w/ mpox patient; 13/22 reported sexual contact

Vakaniaki EH et al. *Nat Med*. [Accepted]

Clade Ib geographic expansion to North Kivu

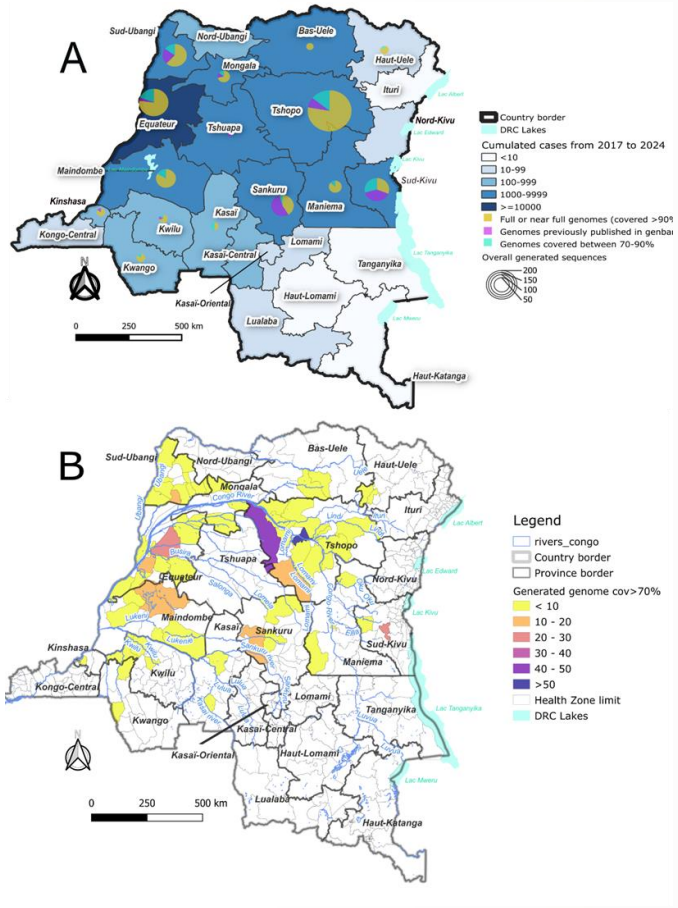


- Recent expansion of Clade Ib from South Kivu to North Kivu
- Initial analysis focused on earliest identified cases and epidemiological mapping of introductions
- Cases identified within internal displacement camps and included suspected transmission b/w children
- Suspected transmission through close non-intimate contacts

Age group (years)	Male	Female	Total
<15	2	1	3
15-30	2	3	5
>30	1	0	1
Total	**5**	**4**	**9**
Hospitalization	3 (60%)	3 (75%)	6 (67%)
Clinical symptoms			
Cutaneous eruptions	5 (100%)	4 (100%)	9 (100%)
Genital eruptions	4 (80%)	3 (75%)	7 (78%)
Oral eruptions	2 (40%)	4 (100%)	6 (67%)
Fever	3 (60%)	3 (75%)	6 (67%)
Headache	4 (80%)	3 (75%)	7 (78%)
Myalgia	5 (100%)	3 (75%)	8 (89%)
Arthralgia	4 (80%)	3 (75%)	7 (78%)
Fatigue	1 (20%)	2 (50%)	3 (33%)
Cervical lymphadenopathy	3 (60%)	4 (100%)	7 (78%)
Inguinal lymphadeonpathy	3 (60%)	2 (50%)	5 (56%)

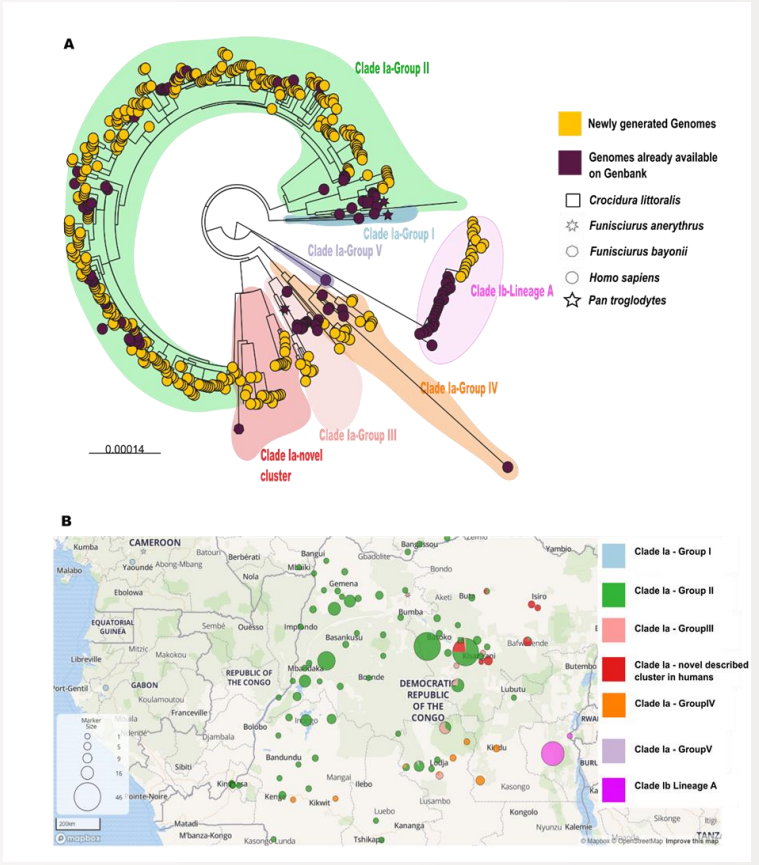
Data not yet published

Longitudinal analysis of Clade Ia MPXV genomes



- Longitudinal analysis of Clade Ia genome sequences from DRC spanning 2018-2024
- 348 MPXV genomes (>90 coverage) from 14/26 provinces
- Data suggests Clade Ia cases continuing to be driven by zoonosis

Clade - group	APOBEC3	Other	Total	Ratio APOBEC3/other	APOBEC3/Total, %
Clade Ia	**195**	**1632**	**1827**	**0.119**	**10.7%**
Clade Ia- Group 1	5	95	100	0.053	5.0%
Clade Ia- Group 2	147	1112	1259	0.132	11.7%
Clade Ia- Group 3	11	145	156	0.076	7.1%
Clade Ia- novel	28	221	249	0.127	11.2%
Clade Ia- Group 4	1	12	13	0.083	7.7%
Clade Ia- Group 5	1	33	34	0.030	2.9%
Overall Clade Ib	**29**	**111**	**140**	**0.261**	**20.7%**
Clade Ib internal branches	23	41	64	0.561	35.9%

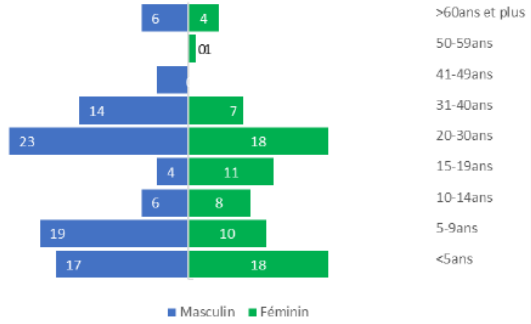


Kinganda-Lusumaki E et al. *Cell* [In Submission] *preprint available

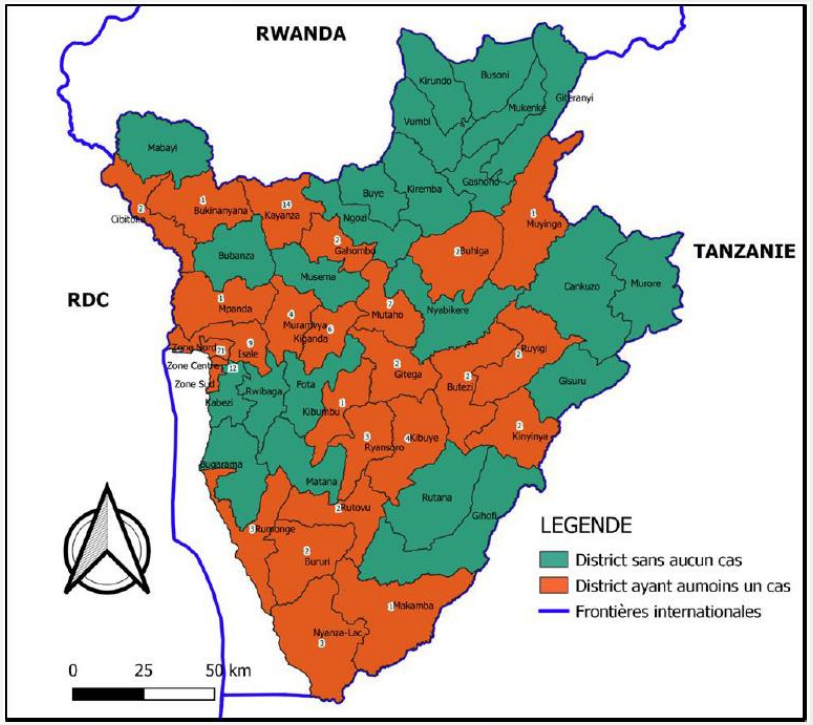
Transboundary movement of Clade I MPXV: DRC -> Burundi

As of 20 August 2024

Nouveaux cas confirmés	10
Cumul de cas confirmés	170
Déchargés	30
Cas actifs	140
Total Décès	00
Nouveaux cas suspects	19
Cas suspects validés après investigation	18
Cumul des cas suspects	624



- Most cases among those 20 to 30 years (24.1%),
- Children <5 years (20.6%) and 5 to 9 years (17.1%) comprise 37.7% of cases overall
- 26/49 districts have at least one confirmed mpox case



Burundi SitRep Ministry of Public Health No. 27 (courtesy of Dr. Alexis Nizigiyimana

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Ongoing Questions for Assessment

- Risk factors for infection and outcomes for Clade Ia and Clade Ib
  - Role of STIs, HIV status, etc
- Ongoing assessment of virus evolution
- Factors contributing to Clade Ia geographic expansion
  - Likely multifactorial but virus evolution also needs to continually be monitored
- Assessment of Clade Ib transmission patterns
- Clade Ib infection and outcome risks for children
- Comparative studies b/w Clade Ib and Clade IIb in vivo
  - E.g. mucosal susceptibilities, virus distribution, etc.
- Increased accessibility for rapid testing, therapeutics, and vaccination in endemic regions

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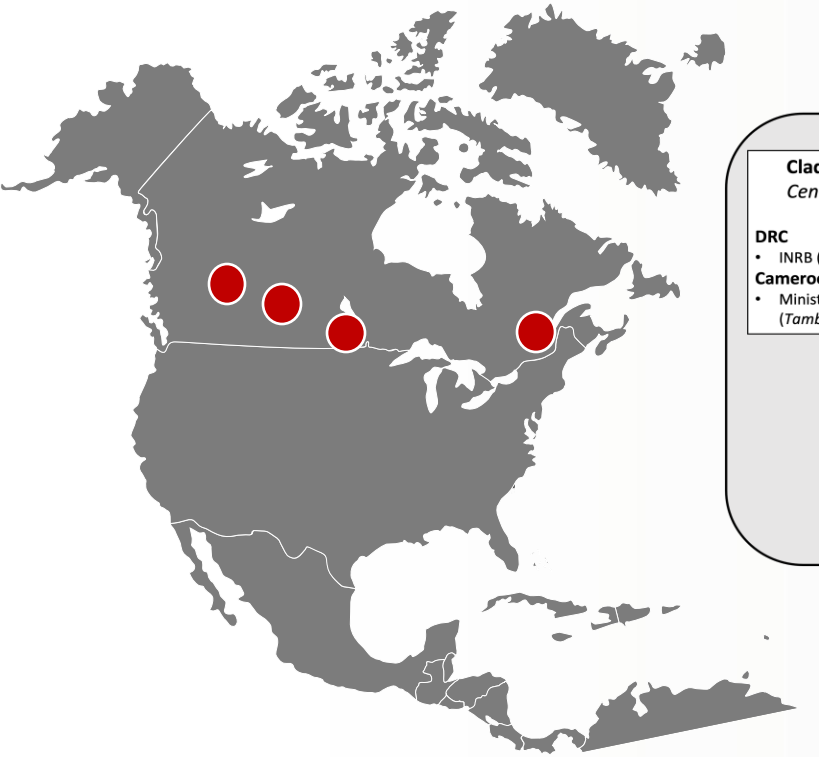
A prospective and retrospective multi-center, cohort study for surveillance, clinical characterization and determination of relative vaccine effectiveness for monkeypox virus clade IIb by the International Monkeypox Response Consortium (IMREC)



Endemic

Clade I MPXV
Central Africa

DRC
- INRB (***Mbala***)

Cameroon
- Ministry of Health (*Tambo*)

Clade IIa MPXV
West/Central Africa

Liberia
- (*Jetoh*)

Sierra Leone
- Njala University (*Ansumana*)

Ghana
- KNUST/ALERTT (*Amuasi*)
- University of Ghana (*Yeboah-Manu*)

Nigeria
- (*Cadmus*)

Cameroon
- Ministry of Health (*Tambo*)

Non-Endemic

Clade IIb MPXV
Global Outbreak
CANADIAN PARTICIPATION

Manitoba
- U Manitoba (***Kindrachuk,*** *Mckinnon, Shaw, Fowke, Lorway, Souleymanov, Keynan*)

Quebec
- McGill University Health Centre/FRQS (*Vinh*)

Saskatchewan
- VIDO/Usask (*Kelvin, Wong*)

Ontario
- U Toronto (*Bogoch, Jha*)

Alberta
- U Alberta (*Evans, Noyce, Saxinger, Meier-Stephenson*)

Not Yet Detected
East/Central Africa

Kenya
- U Nairobi/UM Field office *(Kimani, Mckinnon, Fowke, Lorway)*

Uganda
- *(Castelnuovo)*

Rwanada
- University Teaching Hospital of Kigali *(Bitunguhari)*

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