Genomic epidemiology of MPXV

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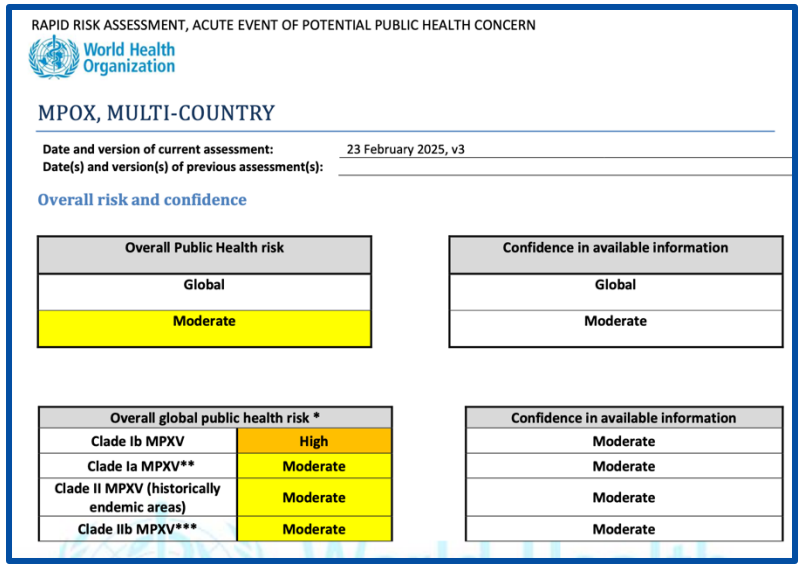
CENTRE FOR PATHOGEN GENOMICS

World Health Organization
Western Pacific Region

IPSN International Pathogen Surveillance Network
WHO hosted network

Introduction to Mpox

- Mpox is a viral illness that spreads between people, mainly through close contact
- It causes painful skin and mucosal lesions, often accompanied by fever, headache, muscle aches, back pain, fatigue, and swollen lymph nodes
- The disease can be debilitating and disfiguring
- Historically a zoonotic disease transmitted from infected animals, Mpox has increasingly shown a tendency to spread between people



RAPID RISK ASSESSMENT, ACUTE EVENT OF POTENTIAL PUBLIC HEALTH CONCERN

World Health Organization

MPOX, MULTI-COUNTRY

Date and version of current assessment: 23 February 2025, v3
Date(s) and version(s) of previous assessment(s):

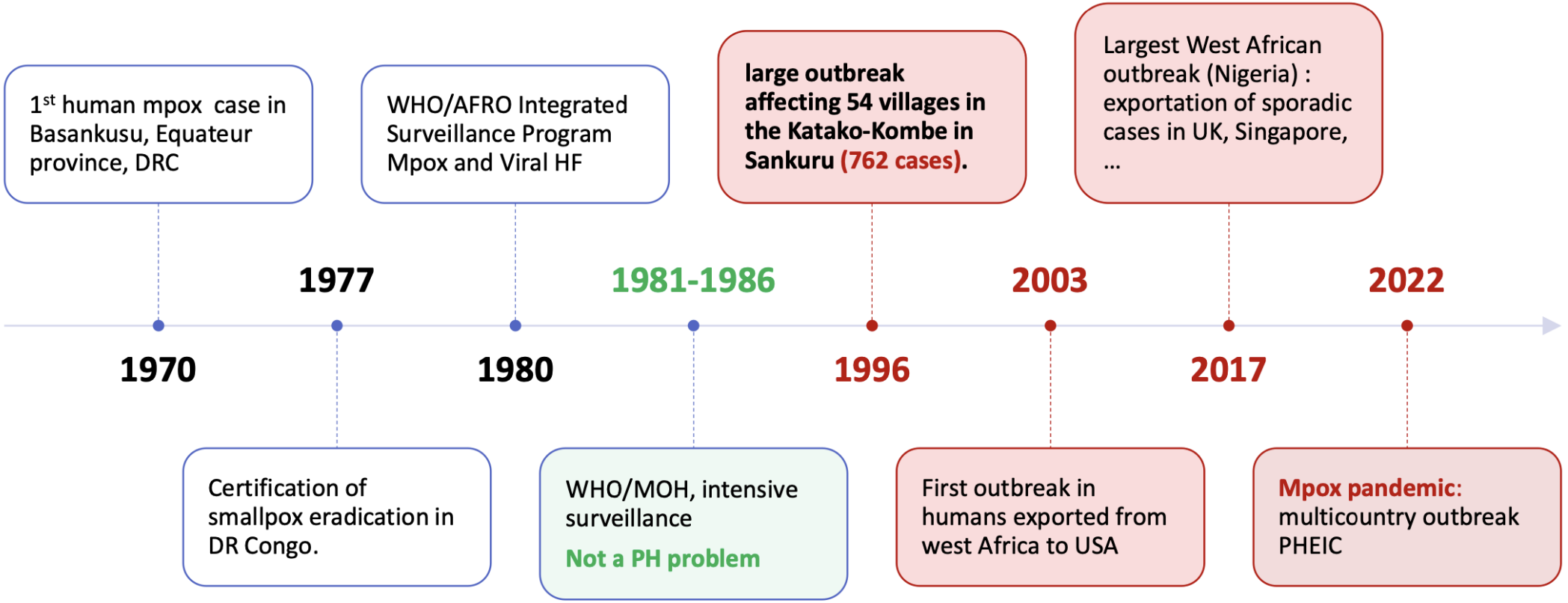
Overall risk and confidence

Overall Public Health risk	Confidence in available information
Global	Global
Moderate	Moderate

Overall global public health risk *		Confidence in available information
Clade Ib MPXV	High	Moderate
Clade Ia MPXV**	Moderate	Moderate
Clade II MPXV (historically endemic areas)	Moderate	Moderate
Clade IIb MPXV***	Moderate	Moderate

WHO Rapid Risk Assessment – Mpox, Global v.3

Mpox surveillance conducted since 1996 in DRC



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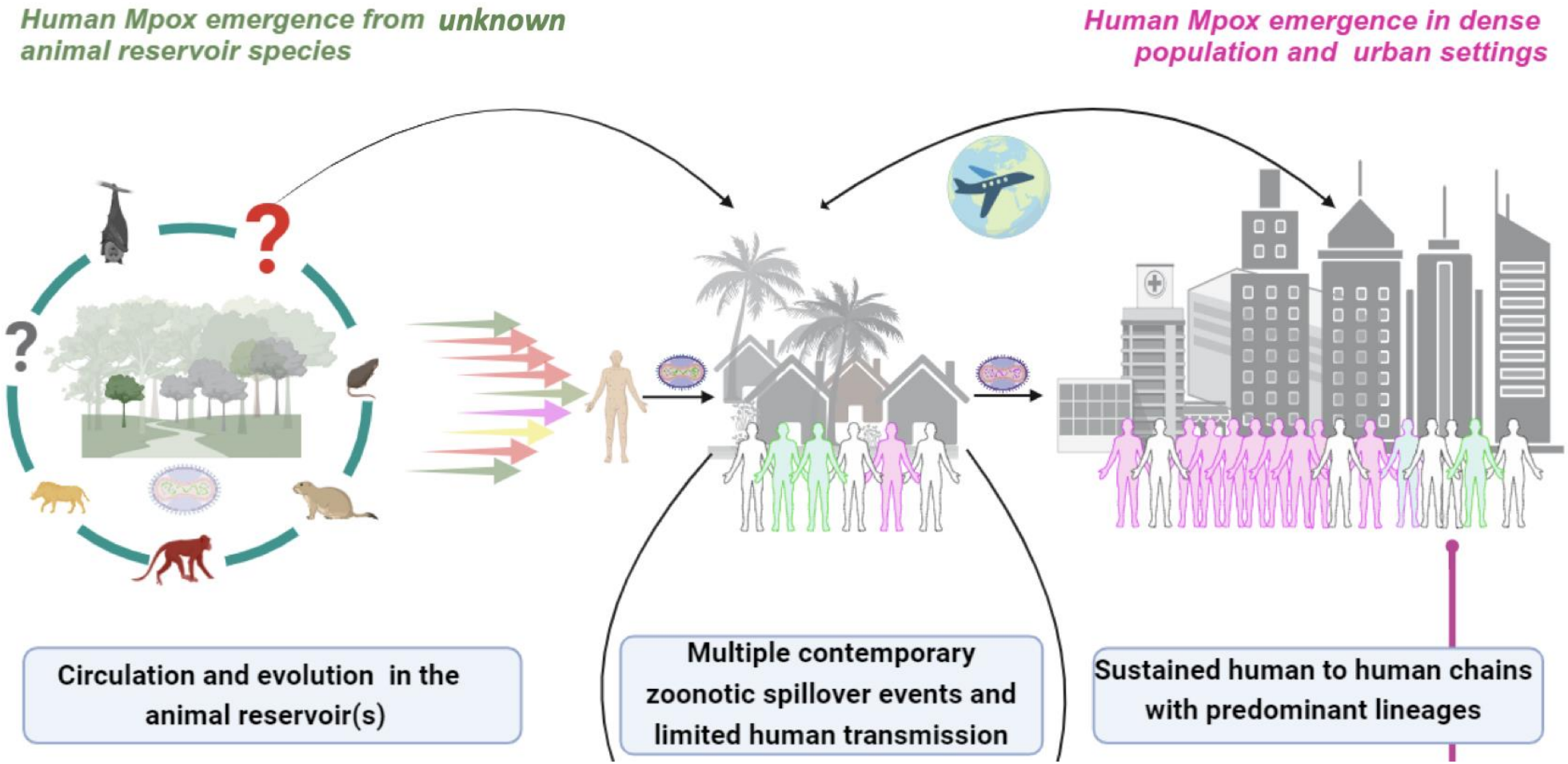
Mpox is a zoonotic infection



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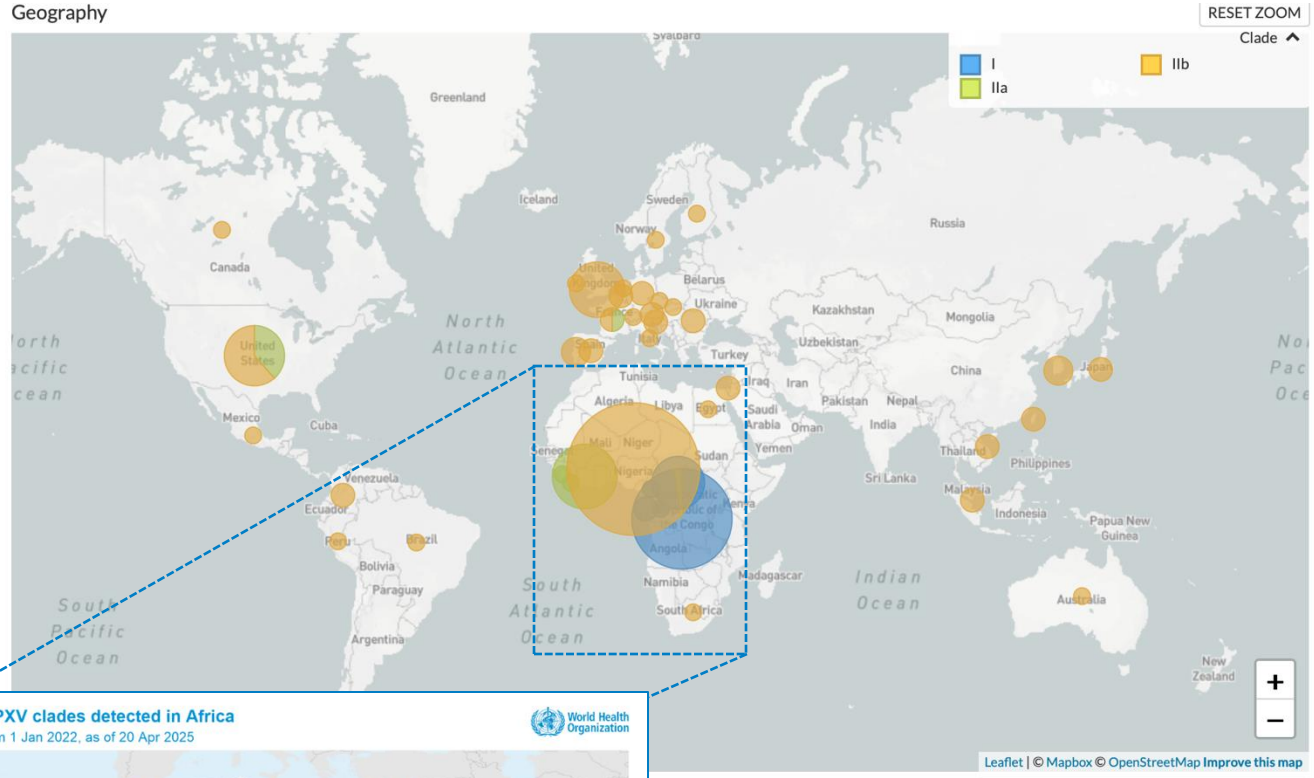
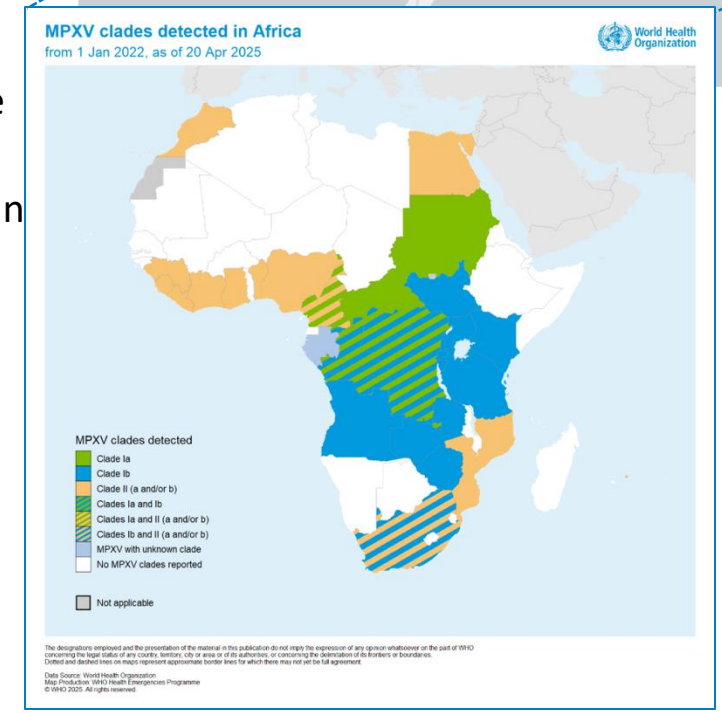
Classification of Mpox

- Mpox is a double-stranded DNA virus, belonging to the *Orthopox* genus of the *Poxviridae* family
- Mpox viruses are classified into two main clades:
  - **Clade I**: endemic in Central Africa, sporadic cases outside of Africa
  - **Clade II**: endemic in West Africa, widespread transmission outside of Africa

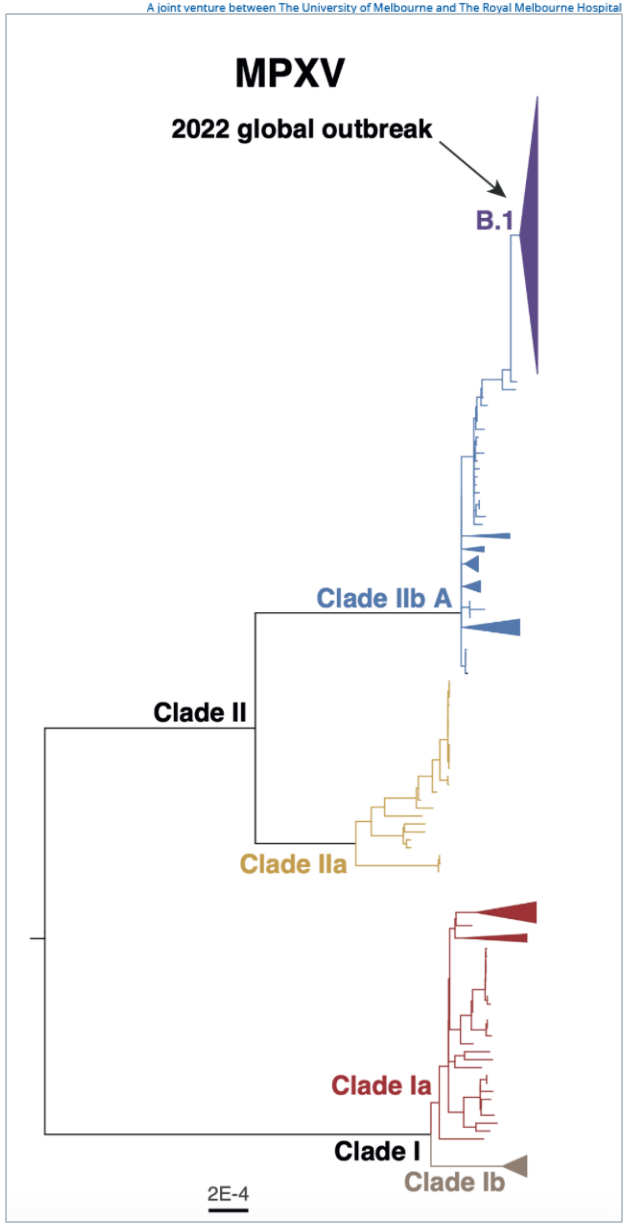




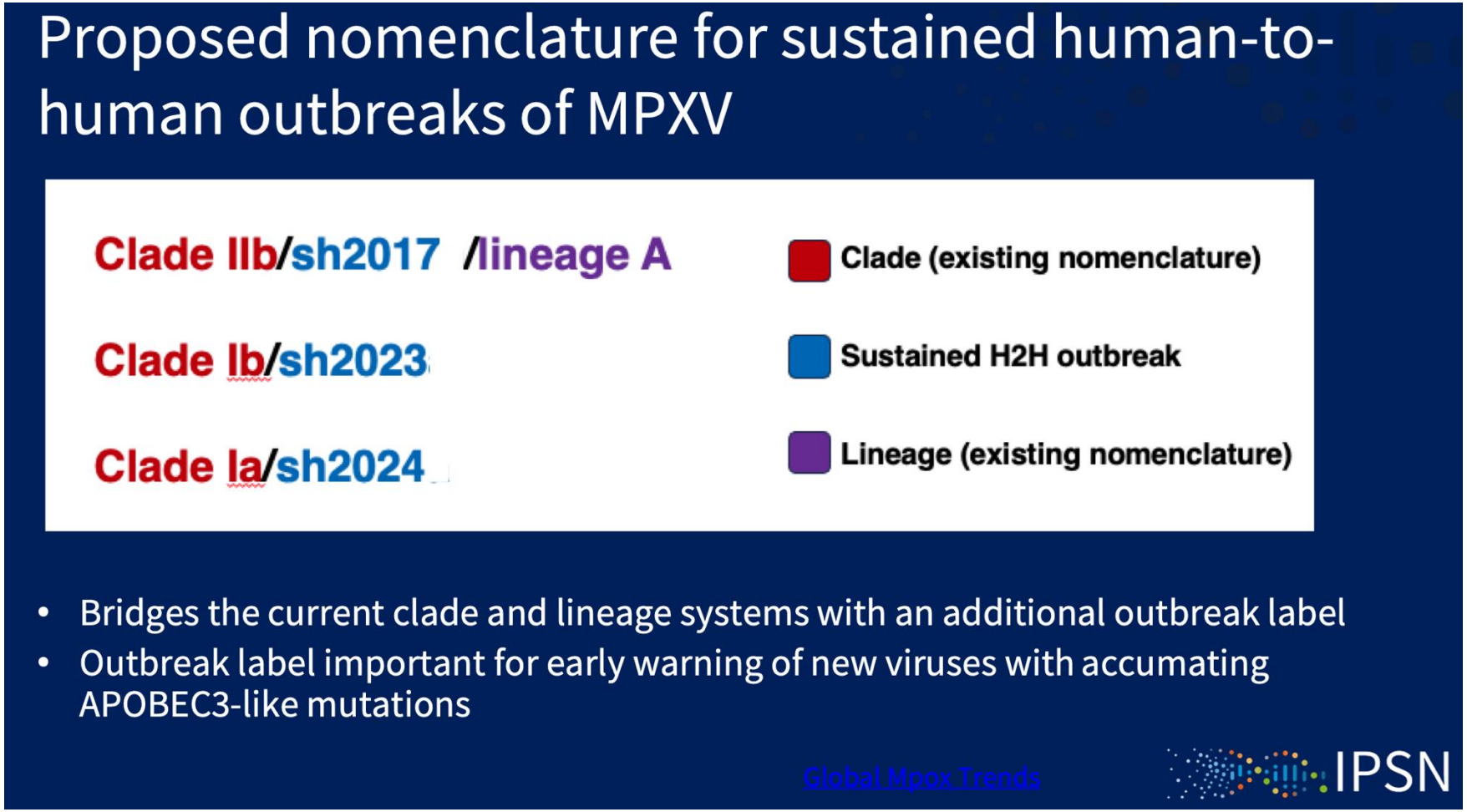
https://nextstrain.org/staging/mpox/all-clades
https://worldhealthorg.shinyapps.io/mpx_global/

Classification of Mpox

- Each clade is divided into two subclades:
  - **Clade I**
    - **Clade Ia**: circulates within multiple countries in Central Africa and is associated with regular spillover from animal reservoirs with some onward human-to-human transmission. Mixing of virus sequences from these countries within the clade Ia phylogenetic tree shows cross-border movement of clade Ia viruses
    - **Clade Ib**: MPXV recently emerged in the eastern part of the Democratic Republic of the Congo and is undergoing sustained human-to-human transmission
  - **Clade II**
    - **Clade IIa**: has historically rarely been isolated and documented in humans. Most available clade IIa genomes were obtained from animal species, and more recent transmission in several West African countries
    - **Clade IIb**: first detected in Nigeria, has undergone extended sustained circulation within humans since at least 2016 and has caused a large ongoing outbreak from 2022 to present. During the global outbreak, it has largely been associated with transmission among men who have sex with men. This outbreak reached its highest peak in August 2022, and continues to circulate at low levels in several countries.



Proposed new nomenclature to convey mode of Mpox transmission



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Outbreak by Clade: Mpox Clade II

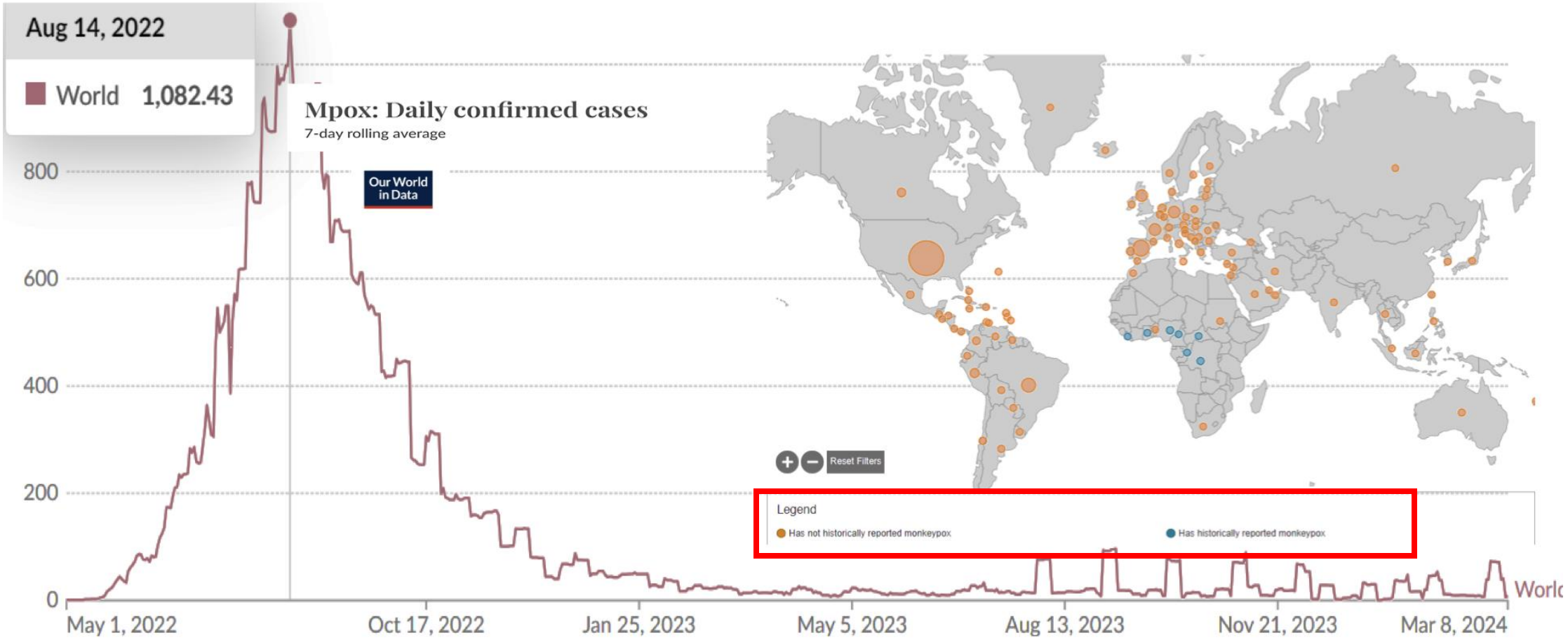
Mpox Clade II: IIa and IIb

- Widespread global transmission, primarily Clade IIB, from May 2022- today
- In May 2022, an outbreak of Mpox appeared suddenly and rapidly spread across Europe, the Americas and then all six WHO regions.
- The global outbreak has affected primarily (but not only) gay, bisexual, and other men who have sex with men and has spread person-to-person through sexual networks.
- Widespread global transmission of Clade IIb resulted in declaration of first WHO Public Health Emergency of International Concern (PHEIC)
- Mpox Clade IIa was rarely detected prior to 2024, and even then, almost solely in animal populations. Human cases of Clade IIa are thought to occur as a direct result of zoonotic spillover events

Mpox Clade IIb epidemiology

- Continues to circulate globally as part of the 2022-2025 multi-country outbreak
  - Peaked in July-August 2022 and declined thereafter
- Outbreaks continue to occur, as the virus is circulating throughout all WHO regions including those that had previously achieved epidemic control
  - Predominant MPXV clade globally
  - Further subdivided into lineages, with lineage B.1 predominating
- Majority of cases continue to occur within linked sexual networks, particularly amongst men who have sex with men
- Complexity of exposure and transmission can impact interpretation of genomic data in the context of Clade IIb epidemiological investigations

Mpox PHEIC 1: 2022



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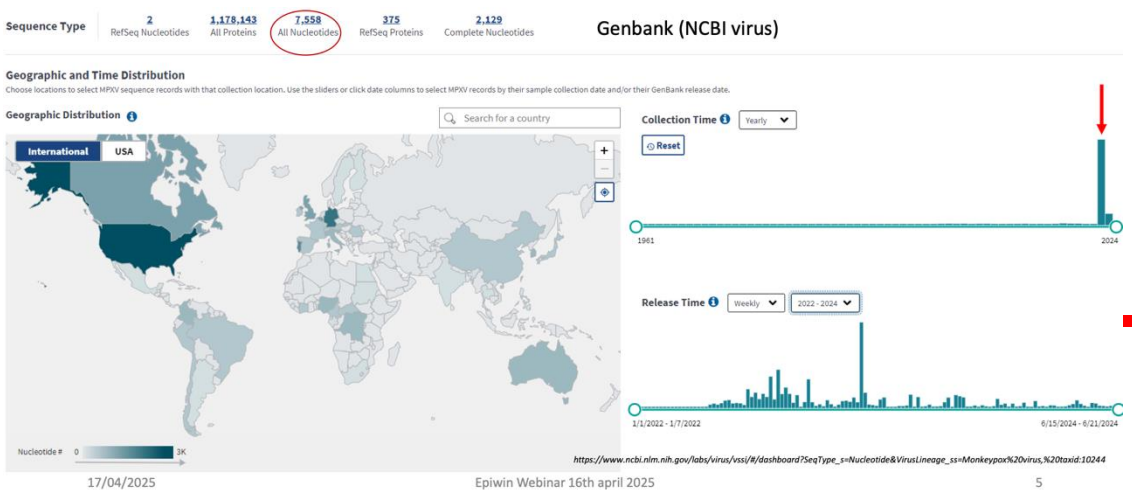
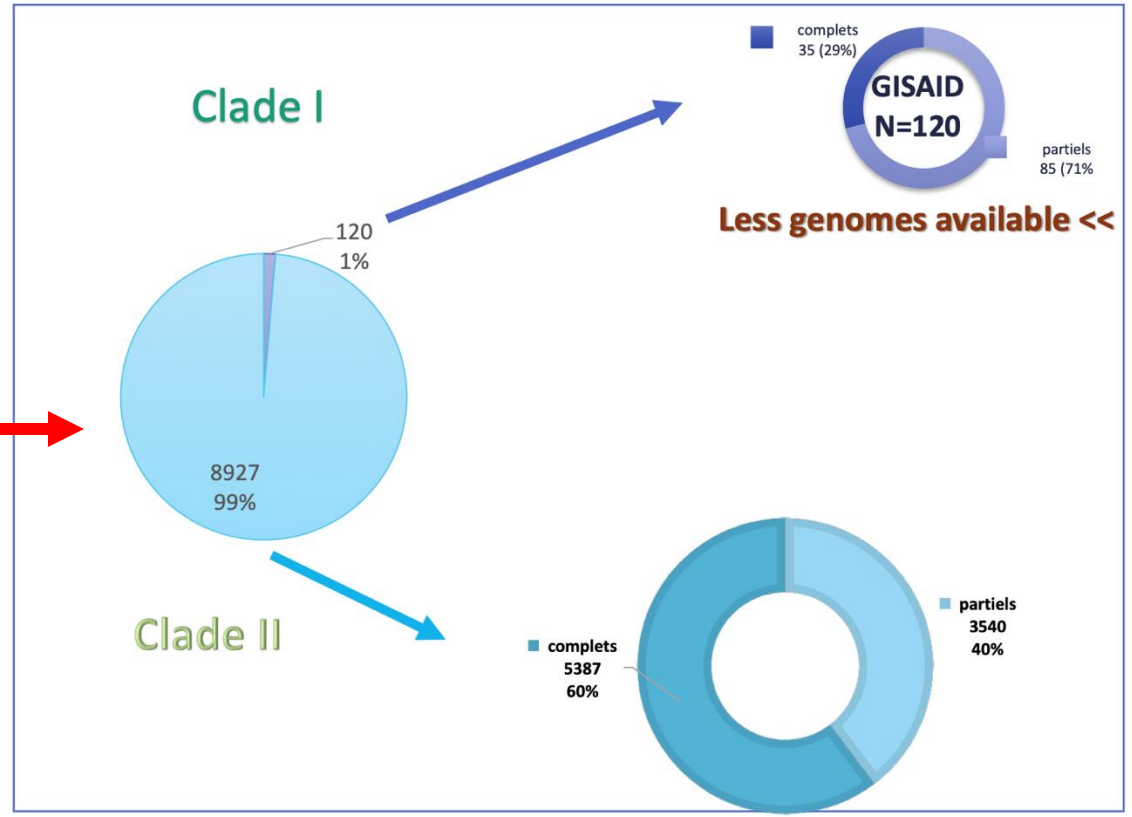
Intensive sequencing: mostly Clade IIb viruses





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Outbreak by Clade: Clade I

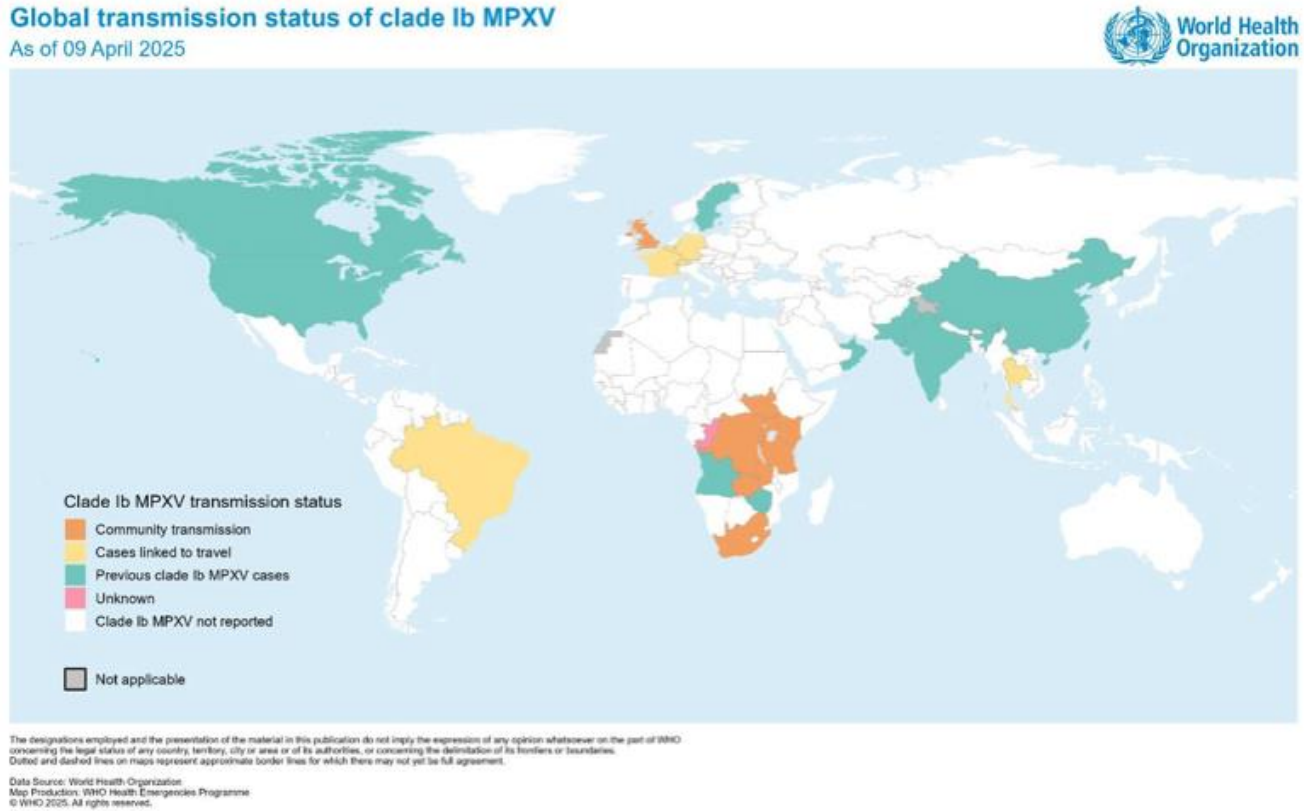
Mpox Clade I: Ia and Ib

- In late 2023, another form of the virus, Clade Ib, began spreading through central Africa via sexual networks, within households and through close contact.
- Initially, concerns of higher case fatality rate following infection with Clade Ib compared to Clade IIb
- Rapid spread and concerns regarding increased severity prompted Africa CDC to declare a Public Health Emergency of Continental Security and the WHO Director-General to declare a second Public Health Emergency of International Concern for Mpox in August 2024.

Clade Ib epidemiology

- Predominantly spreading through the DRC
- Outside DRC, mostly travel-associated cases
  - Secondary cases resulting from importation have been reported
- No zoonotic links, current transmission is human-to-human
- Current WGS data suggests all global Ib cases linked to index strain identified in 2023 in South Kivu
- Clade Ib can spread within sexual networks as well as close physical contact in households, resulting in an increasing proportion of cases in young children

Figure 2. Clade Ib monkeypox virus transmission status by country, as of 9 April 2025



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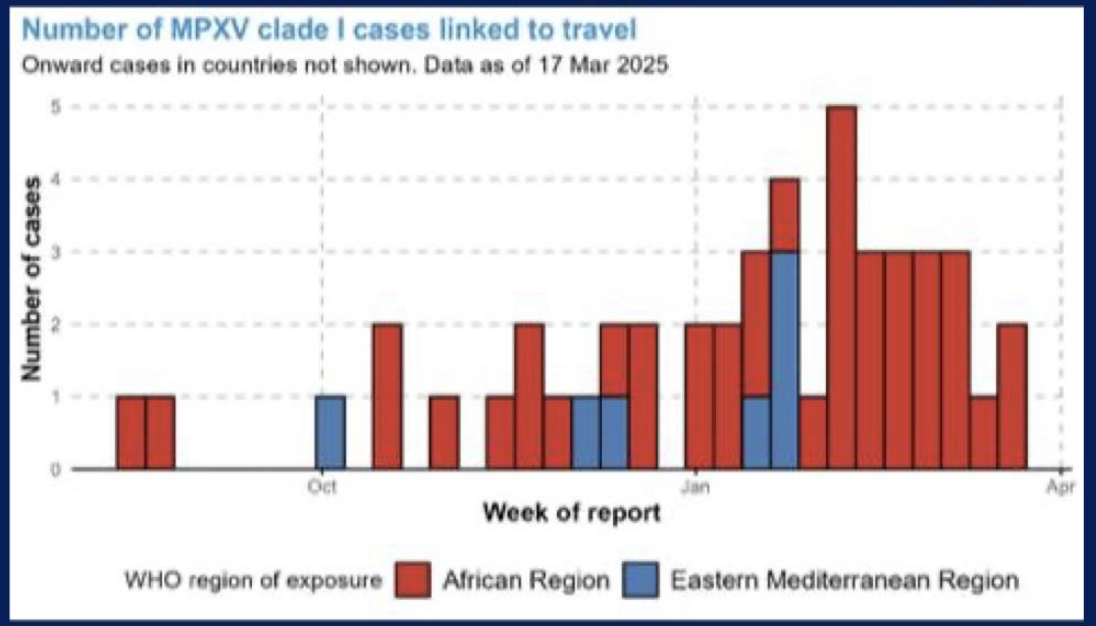
Global snapshot: Clade Ib epidemiology

Continued circulation of clade Ib MPXV

Clade Ib MPXV cases

Country[1]	WHO Region	Cases since Jan 2024	Cases in past 6 weeks	Transmission status[2]
Democratic Republic of the Congo	African Region	[3] 18 013	[3] 1134	Community transmission
Uganda	African Region	4141	1504	Community transmission
Burundi	African Region	3645	286	Community transmission
Rwanda	African Region	104	2	Community transmission
Kenya	African Region	55	18	Community transmission
Zambia	African Region	31	13	Community transmission
United Republic of Tanzania	African Region	22	22	Community transmission
South Africa	African Region	6	6	Community transmission
The United Kingdom	European Region	10	2	Cases linked to travel
Germany	European Region	8	1	Cases linked to travel
China	Western Pacific Region	7	0	Cases linked to travel
Belgium	European Region	5	1	Cases linked to travel
Thailand	South-East Asia Region	4	0	Cases linked to travel
United States of America	Region of the Americas	4	2	Cases linked to travel
Qatar	Eastern Mediterranean Region	3	3	Cases linked to travel
South Sudan	African Region	3	3	Cases linked to travel
Angola	African Region	2	0	Cases linked to travel
France	European Region	2	1	Cases linked to travel
Canada	Region of the Americas	1	0	Cases linked to travel
India	South-East Asia Region	1	0	Cases linked to travel
Oman	Eastern Mediterranean Region	1	0	Cases linked to travel
Pakistan	Eastern Mediterranean Region	1	0	Cases linked to travel
Sweden	European Region	1	0	Cases linked to travel
United Arab Emirates	Eastern Mediterranean Region	1	1	Cases linked to travel
Zimbabwe	African Region	1	0	Cases linked to travel
Brazil	Region of the Americas	1	1	Cases linked to travel



- Continuous exportation of clade Ib cases;
- 26 countries reported at least clade Ib case; 8 African countr have community transmission

Global Mpox Trends

https://cdn.who.int/media/docs/default-source/crs-crr/epiwin_mpox_genomics_2025.pdf?sfvrsn=357bb6a9_2

First mpox clade Ib confirmed in Australia

The first case of mpox clade Ib in Australia is a timely reminder to at-risk population groups to get vaccinated. The risk of community transmission from this case is low. However, the Australian Government is monitoring the situation.

16 May 2025 News

Clade Ib epidemiology

- Clade Ib infection can be particularly severe amongst:
  - Immunocompromised individuals (those living with uncontrolled HIV-1)
  - Children, pregnant women and their unborn babies

- Given the continued expansion of Clade Ib, significant under-detection particularly amongst high-risk groups and current inadequate control capacity, the risk of ongoing national and international spread remains high. The overall public health risk posed by Clade Ib in the most-affected countries has been assessed by WHO as **High**

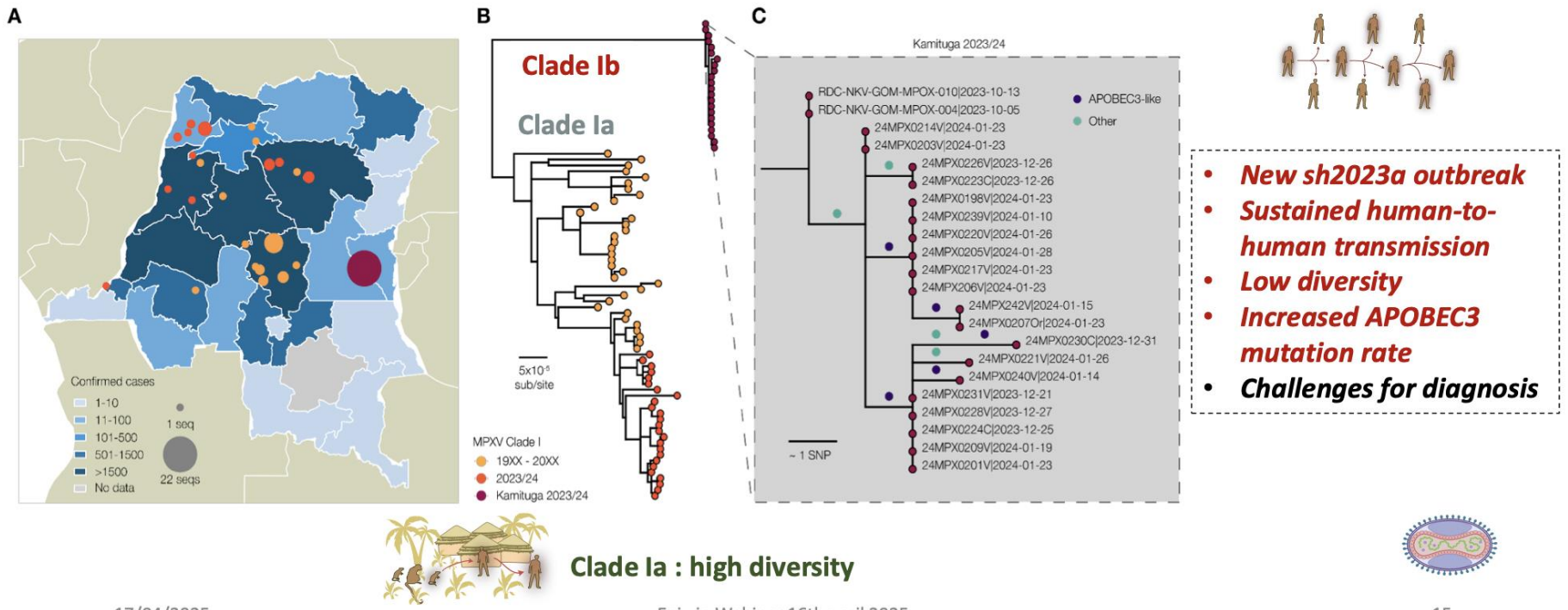
Clade Ia epidemiology

- Based on current understanding, Clade Ia has a higher case-fatality rate (CFR) than Clade Ib Mpox.
  - CFR differ between endemic and non-endemic areas
  - Unclear whether higher CFR in endemic compared to non-endemic areas reflects underlying differences in populations (malnutrition, co-infections, barriers to health care access), limitations of surveillance, or characteristics of the virus itself
- In Central Africa, human Clade Ia infection has occurred through contact with infected dead or live wild animals, household transmission, or patient care
  - High proportion of cases have been reported in children younger than 15 years of age
- Emergence of additional cases in urbanized centres, outside of endemic areas in Africa, has raised concerns about potential for international spread
- Overall public health risk posed by Clade Ia has been assessed by WHO as **Moderate**, largely due to higher mortality observed in endemic areas. Potential for regional and international spread is considered more moderate compared to Clade Ib

High diversity of Clade Ia, likely due to zoonotic introductions

Brief Communication | Published: 13 June 2024

Sustained Human Outbreak of a New MPXV Clade I Lineage in the Eastern Democratic Republic of the Congo



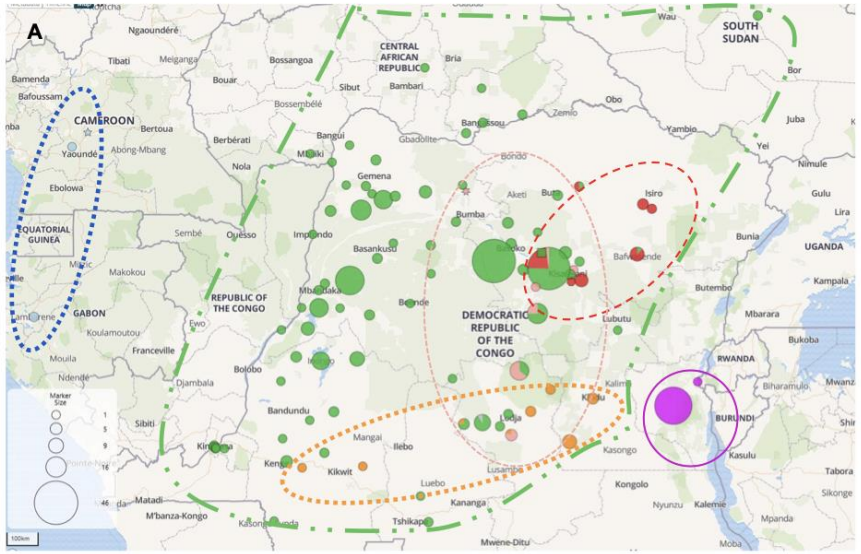
- *New sh2023a outbreak*
- *Sustained human-to-human transmission*
- *Low diversity*
- *Increased APOBEC3 mutation rate*
- *Challenges for diagnosis*

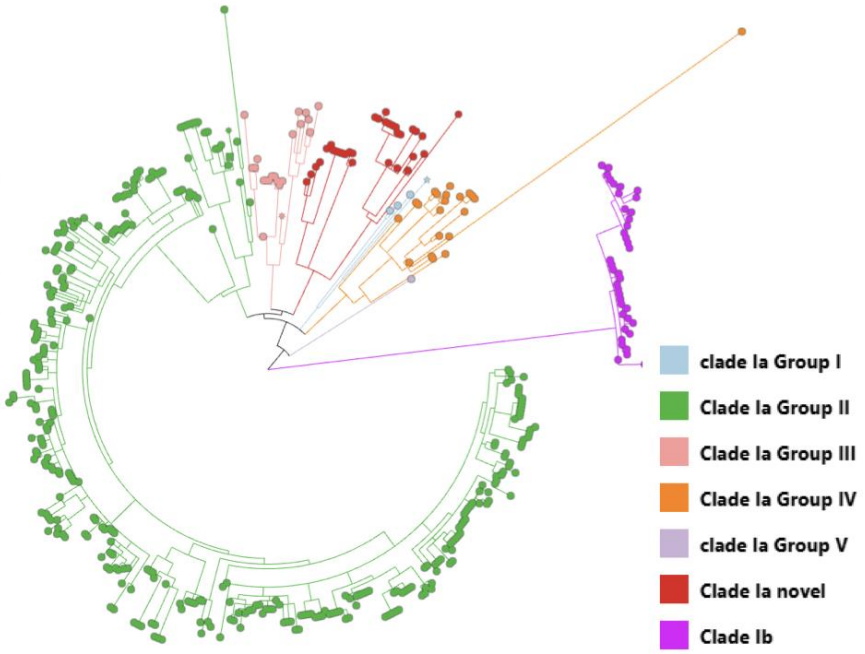
Clade Ia : high diversity

https://cdn.who.int/media/docs/default-source/crs-crr/epiwin-webinar-eddykl-april2025.pdf?sfvrsn=7d8d996c_1

High diversity of Clade Ia, likely due to zoonotic introductions

High diversity of mpox clade I in the DRC

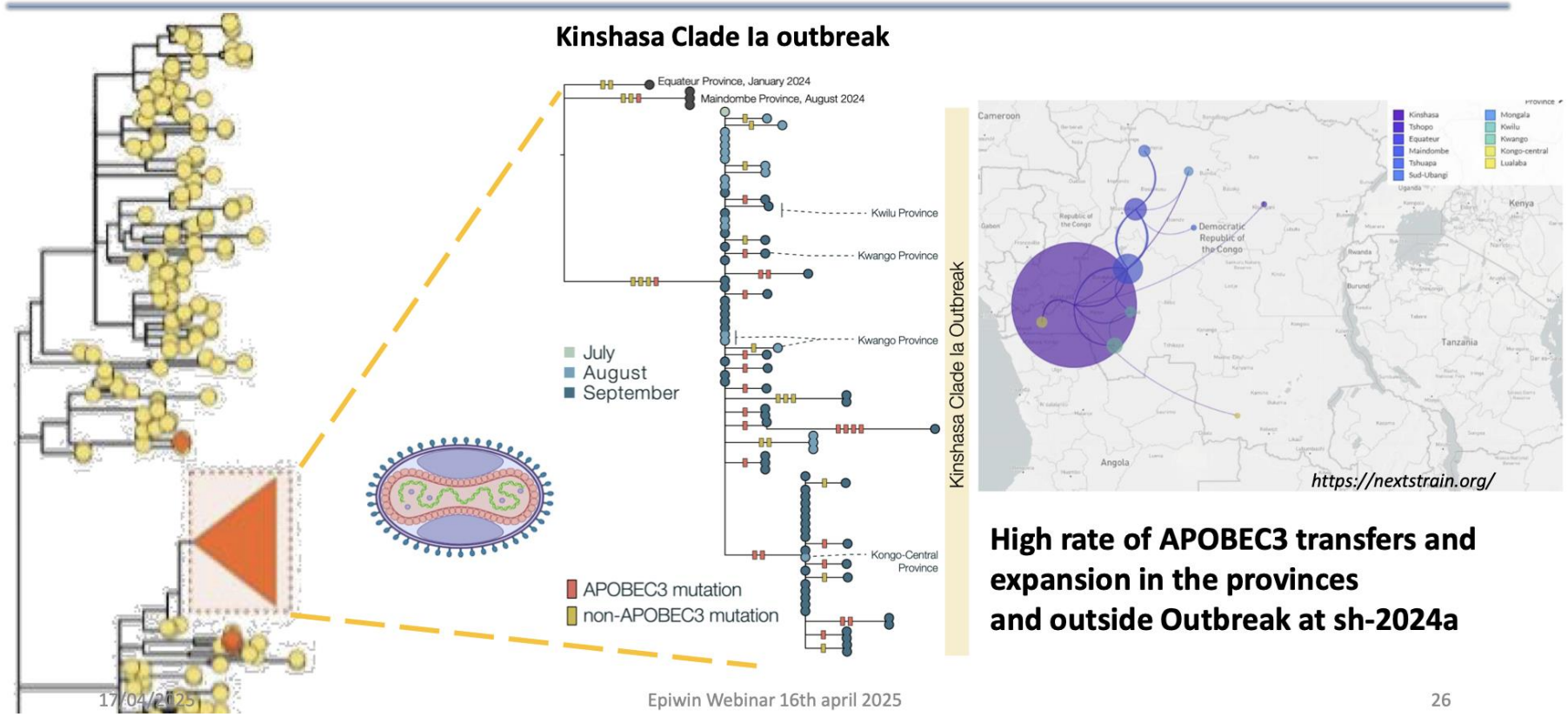




- Phylogeographic Clusters
  - Cameroon and Gabon western (Group I)
  - Sankuru, Maniema and Kwilu most southern (savannah)

https://cdn.who.int/media/docs/default-source/crs-crr/epiwin-webinar-eddykl-april2025.pdf?sfvrsn=7d8d996c_1

Outbreak of Clade Ia in DRC capital



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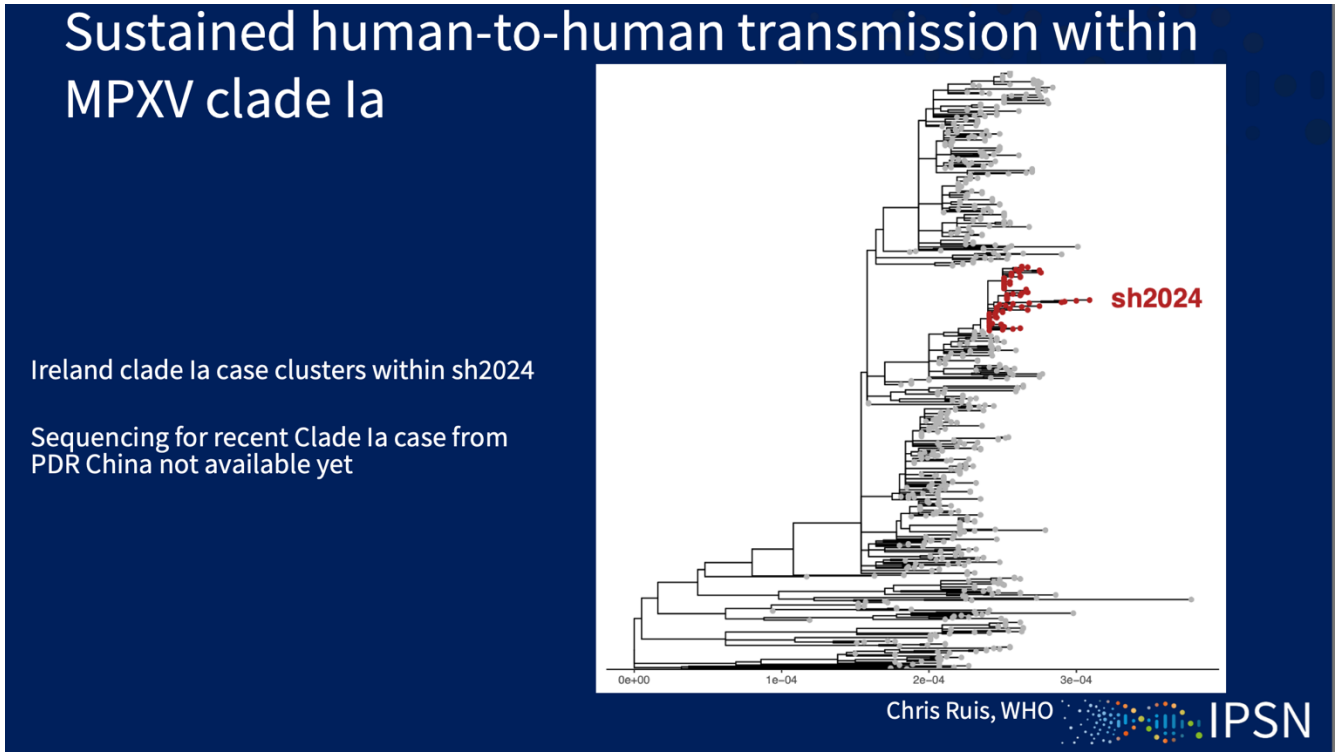
Global snapshot: genomic epidemiology of Clade Ia

- Primarily detected in the DRC, with recent evidence suggesting transmission occurring in provinces the virus wasn't previously found (including capital city Kinshasa)
- Sporadic cases in neighboring countries
- Historically resulting from zoonotic spillover, recent evidence of human-to-human transmission of one Clade Ia lineage since 2024, primarily through sexual contact, in Kinshasa
- One travel associated case has been detected in Ireland and in China, both belong to cluster with DRC Clade Ia lineage sequences



https://cdn.who.int/media/docs/default-source/crs-crr/epiwin_mpox_genomics_2025.pdf?sfvrsn=357bb6a9_2

Using genomics to answer public health questions for Mpox

Application of genomics to investigate Mpox

- Wherever Mpox outbreaks are not rapidly contained and human-to-human transmission is not limited, there is a potential risk of sustained community transmission
- It is of public health interest to rapidly identify and link cases to understand community transmission and prevent further spread
- Genomics is a tool that can be used as part of these investigations
- Majority of community cases outside of Africa continue to belong to Clade IIb
- Must be aware that introductions of other clades and sub-clades from endemic into non-endemic countries can occur

Public health questions: can genomics address these for Mpox?

- **Are cases linked/exposed to the same source?**
- Is the viral lineage/sub-clade novel?
- Will the vaccines/diagnostic tests/antivirals still work?
- Is the lineage/sub-clade associated with severe disease?

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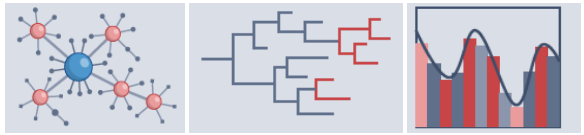
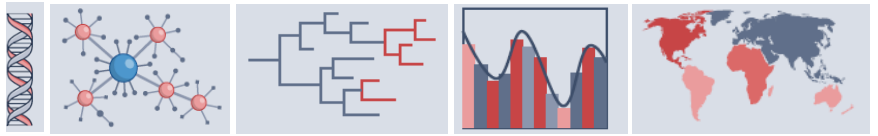
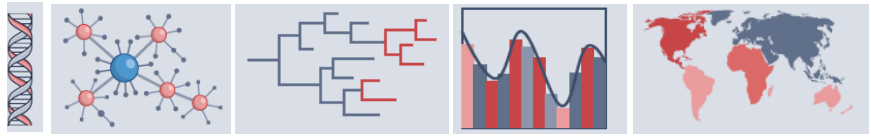
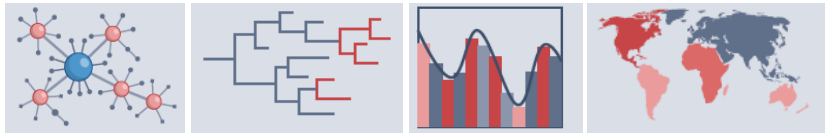
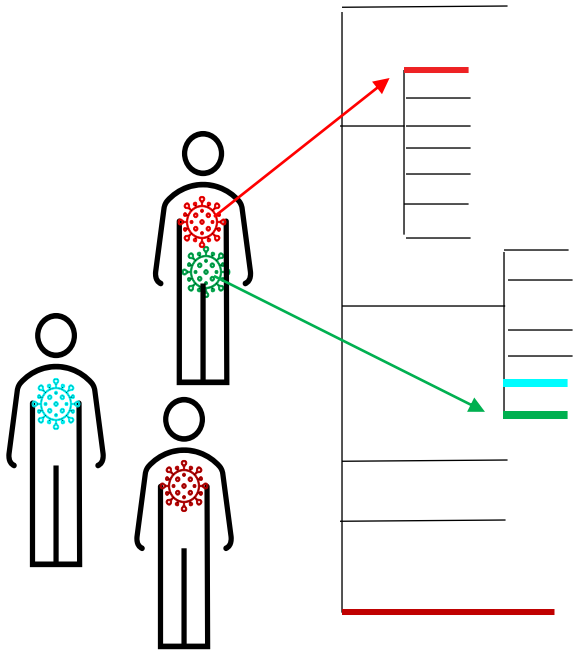
	
	
	
	

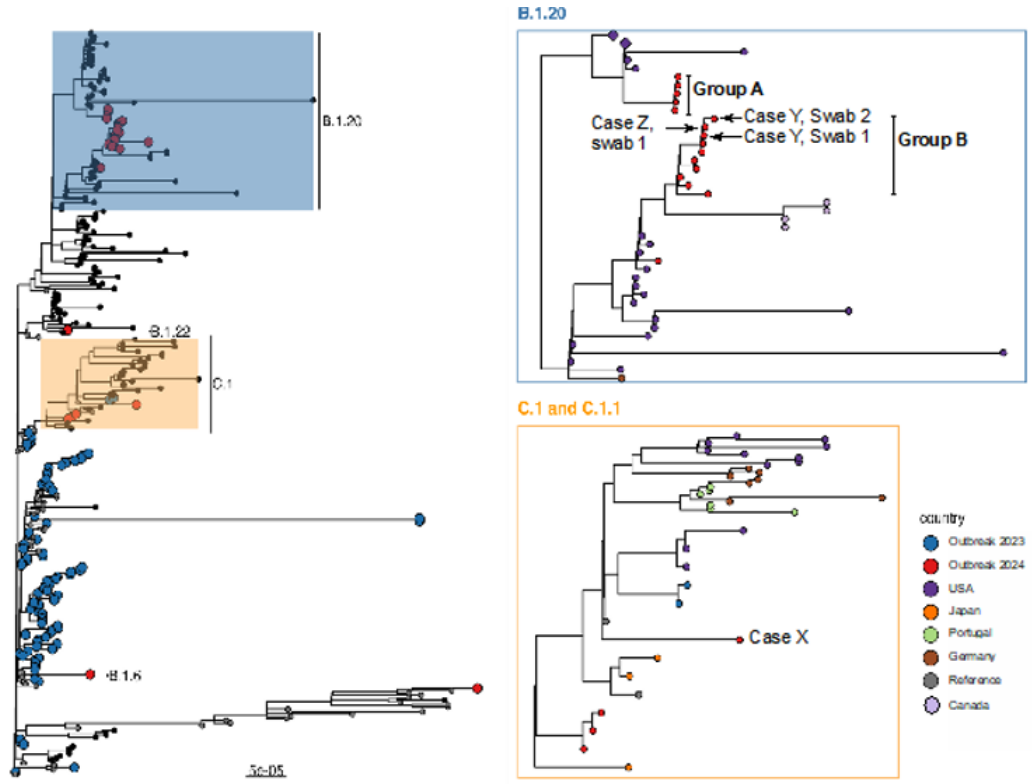
Key considerations when attempting to link Mpox cases using genomic epidemiological data



One case > one distinct consensus (i.e. Mpox)

- Directly linking cases cannot be conducted using genomics alone and genomic data must be interpreted in epidemiological context
- Lack of global genomic surveillance and bias in geographical representation limits geographical source attribution and understanding of currently circulating lineages
- Genomic relatedness between cases should only be attributed to a common exposure(s) rather than direct link(s) in the absence of robust epidemiological evidence
- Within-host diversity: multiple sub-lineages and sequence diversity have been detected from different bodily sites within the same host, potentially related to complexity of transmission
- A genomic threshold for relatedness between cases has not been determined. Genomic relatedness is confounded by ongoing viral evolution, within and between hosts, and presence of large genome deletions which limits available genomic data for comparison.

Example from Mpox investigation: Melbourne 2024



- In April and May, 2024, genomic surveillance helped to identify five clade IIb lineages (B.1.6, B.1.20, B.1.22, C.1, and C.1.1) among 19 newly detected mpox cases in Victoria
- Genomes obtained from two different cases (swab 1, case Y and swab 1, case Z) were more closely related than those obtained from different anatomical sites in the same case (case Y, swab 1 and swab 2)
- Therefore, due to the high degree of within-host diversity, genomic data alone cannot be used to reliably confirm links between cases without robust epidemiological data.
- Instead, genomic data should be used as a complementary tool alongside epidemiological investigations to identify a common source of exposure.

https://www.thelancet.com/journals/lanmic/article/PIIS2666-5247(24)00267-2/fulltext

Public health questions: can genomics be used address these for Mpox?

Question

- Are cases linked/exposed to the same source?

Data you need

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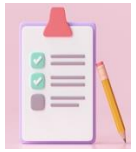	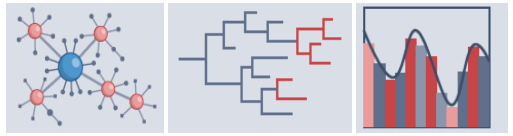

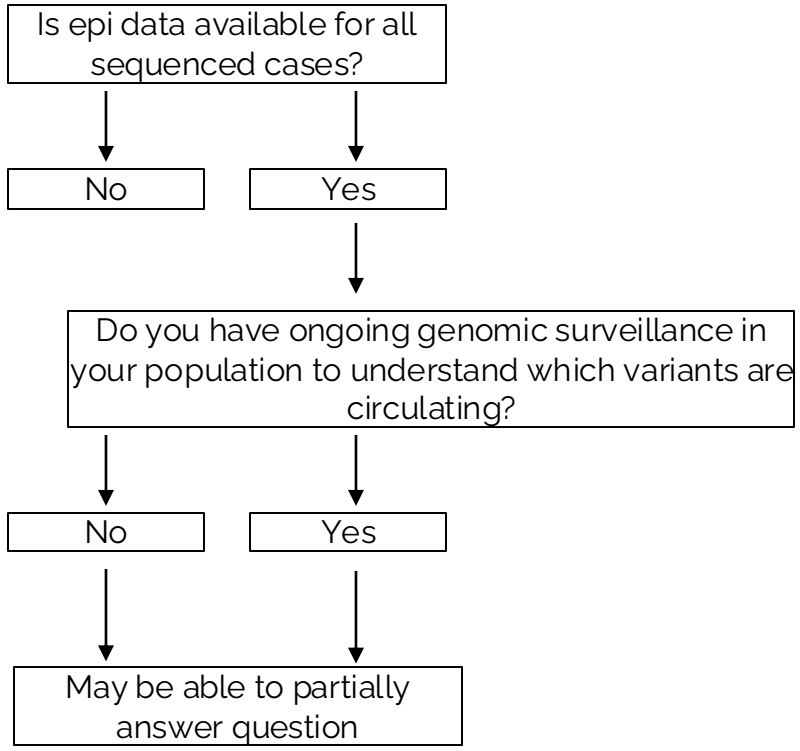

- Without ongoing genomic surveillance, cannot be certain that cases weren't infected with predominant community variant, rather than direct transmission/common exposure
- Different consensus sequences can be obtained from different bodily sites

Public health questions: can genomics be used to address these for Mpox?

- Are cases linked/exposed to the same source?
- **Is the viral lineage/sub-clade novel?**
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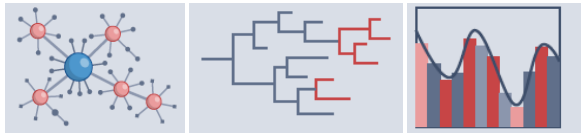
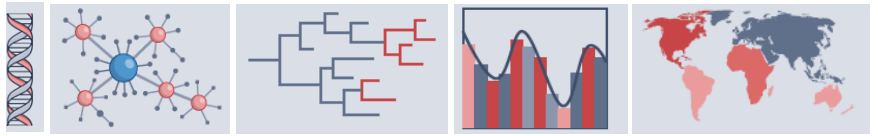
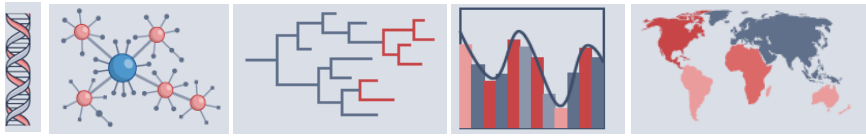
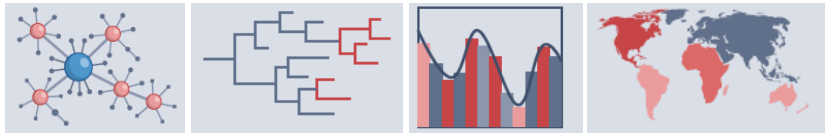
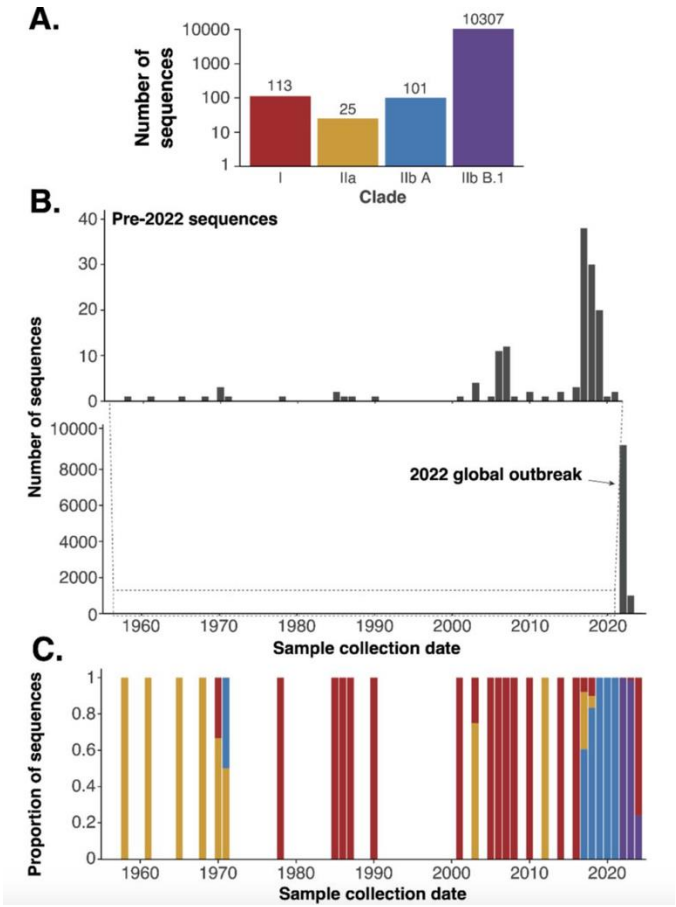
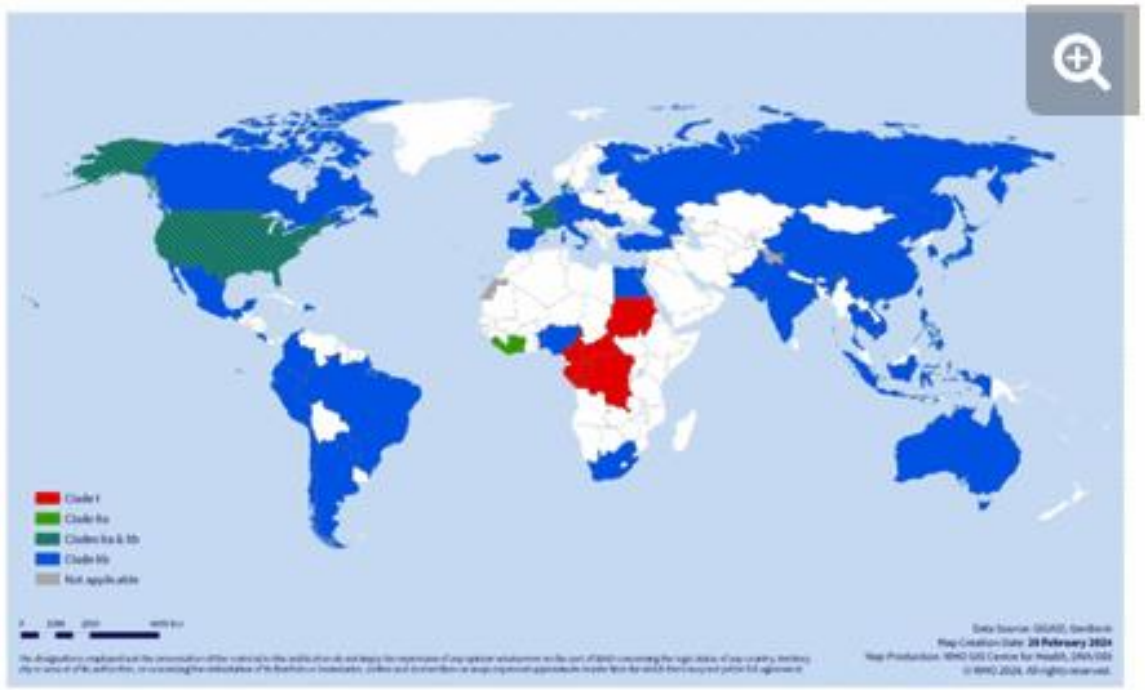
	
	
	
	

Limitations of global Mpox genomic surveillance

Availability of sequences over time



Availability of geographically representative sequences



https://www.nature.com/articles/s41591-024-03370-3

Key considerations when attempting to contextualise a novel/emergent Mpox variant

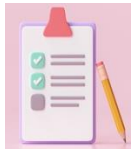
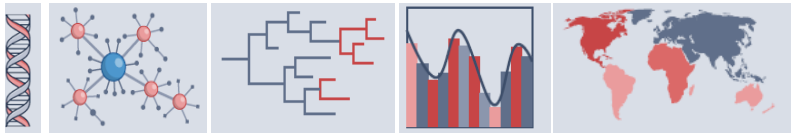
- Lack of global genomic surveillance and bias in geographical representation limits geographical source attribution and understanding of currently circulating lineages
  - You may not be able to know with certainty where the variant emerged or be sure it isn't circulating elsewhere
- Small number of countries contribute the majority of sequences
- You can convey the likelihood of whether a variant is newly introduced into your population or newly emerged by communicating caveats:
  - 'Based on comparisons with data that are currently publicly available/have been generated from my population….'

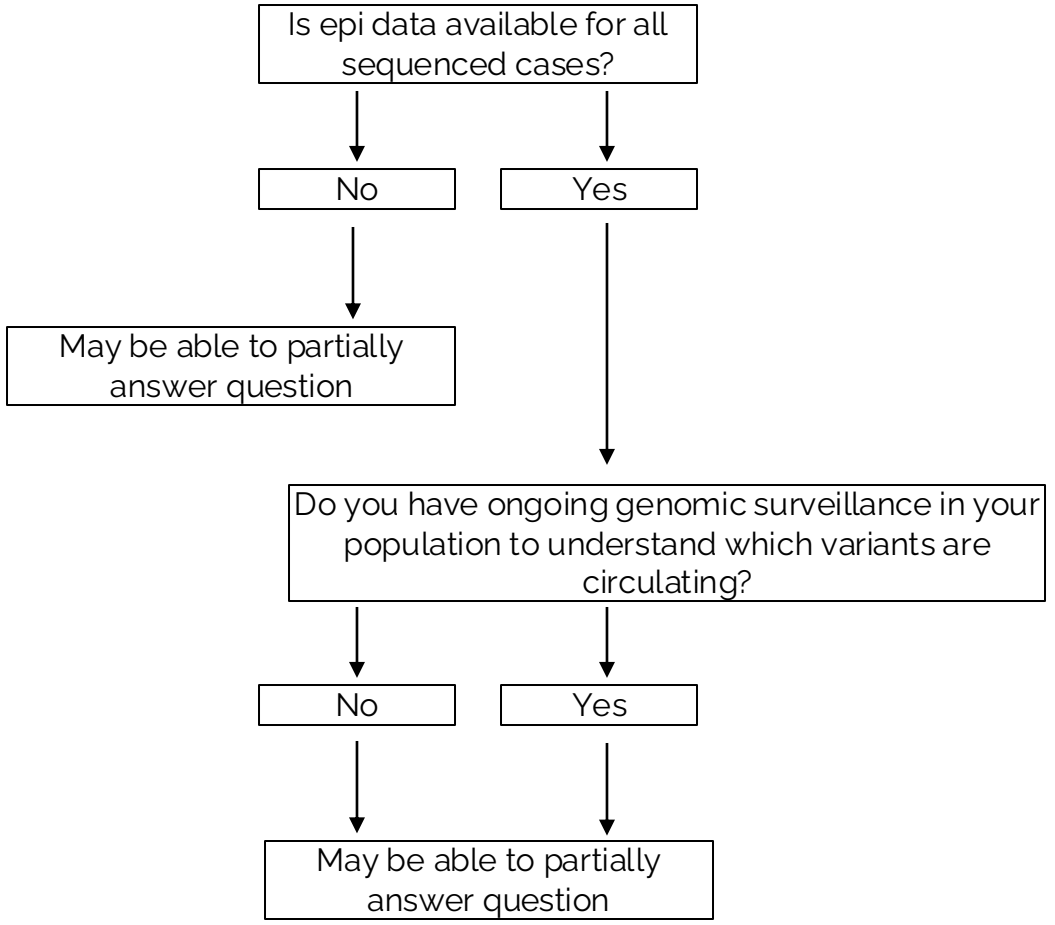
Public health questions: can genomics be used to address these for Mpox?

Question

- Is the viral lineage/sub-clade novel?
  - In my population
  - New variant of the virus

Data you need

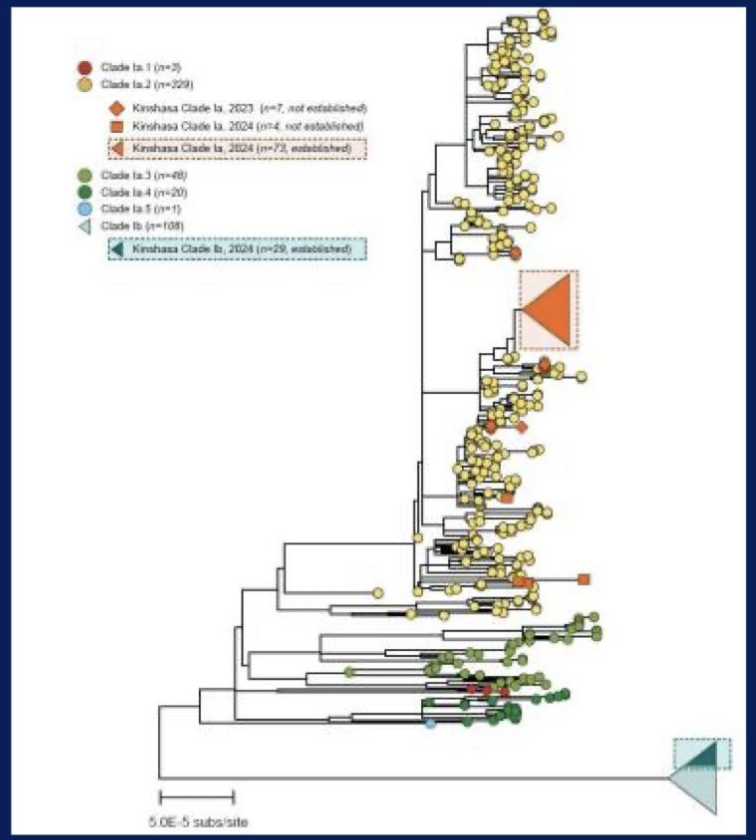
Epi	Genomic
	



Gaps in local/global genomic surveillance may make confirmation of a new variant challenging

Additional uses of genomic data to further understanding of Mpox transmission and spread

Inferring type of transmission from genetic data



- Researchers identified specific mutations in the virus's genome that are characteristic of editing by human APOBEC3 enzymes—proteins that can induce mutations in viral DNA.
- These mutations have been accumulating since at least 2016 in Nigeria, suggesting that MPXV has been transmitting among humans for several years, rather than being solely a zoonotic infection from animal reservoirs
- This finding indicates a shift in the virus's transmission dynamics, highlighting the importance of monitoring its evolution and spread in human populations.

O'Toole et al Science 2023; Kinganda-Lusamaki et al Cell 2024; Wawina Bokalanga et al Lancet accepted

IPSN

Additional uses of genomic data to further understanding of Mpox transmission and spread

- Mpox genomics allows us to infer about which viruses spread through sustained human-to-human transmission
- For mpox, 3 strains have signatures of sustained human-to-human transmission (clade IIb/sh2017; clade Ib/sh2023 and clade Ia/sh2024)
- Genomics has been instrumental for
  - early warning of new variants with potential to spread
  - diagnostic preparedness to clade Ib (supported by the WHO Biohub and WHO EQA programme)
- Coming soon: two WHO (in collaboration with IPSN) documents on genomics (one generic, one mpox-specific)

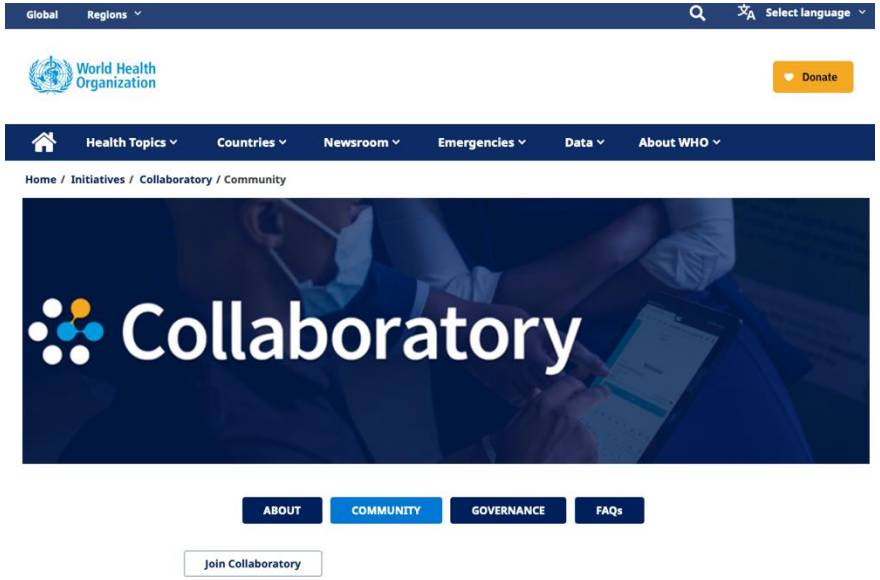
Discussion

- Significant progress has been made in understanding human-to-human transmission of MPXV since 2022, however significant gaps remain:
  - Detailed epidemiological understanding of ongoing outbreaks caused by different clades in the DRC remain poorly understood
  - Transmission dynamics, key drivers, the potential for human-to-human spread through different modes of transmission and the role of asymptomatic infections
  - Risk factors for severe disease, immunity generated following infection and the potential for recurrence or reinfection
  - Little is known about animal reservoirs, incidental hosts, zoonotic transmission or the contribution of spillover events
- Public health risk posed by MPXV varies within different areas across Africa and the world
- MPXV variants can increasingly be expected to find their way into human populations as adaptation to facilitate human-to-human spread increases
- The global population is almost entirely susceptible to orthopoxviruses following eradication of smallpox

Conclusions

- Whilst Clade IIb is the predominant clade globally, all countries remain at risk of importation of all MPXV clades
- Given the high likelihood that existing and new MPXV variants will continue to emerge and spread, coupled with the potential consequences of such events, the current global public health risk at the global level is assessed by the WHO as **Moderate**
- Cryptic transmission, or silent circulation, poses a risk in countries with less robust public health measures in place to detect and investigate imported or locally acquired MPXV cases
- Ongoing genomic surveillance is crucial to monitor the emergence of novel variants, to ensure that therapeutics and diagnostic tools continue to be effective
- More representative sampling methods, such as wastewater surveillance, are required to complement existing surveillance techniques to understand the magnitude of MPXV spread within populations

Resources



https://www.who.int/initiatives/collaboratory/community

Analytical Considerations for Genomic Surveillance of MPXV document hopefully to be circulated by WHO in 2025

THANK YOU

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