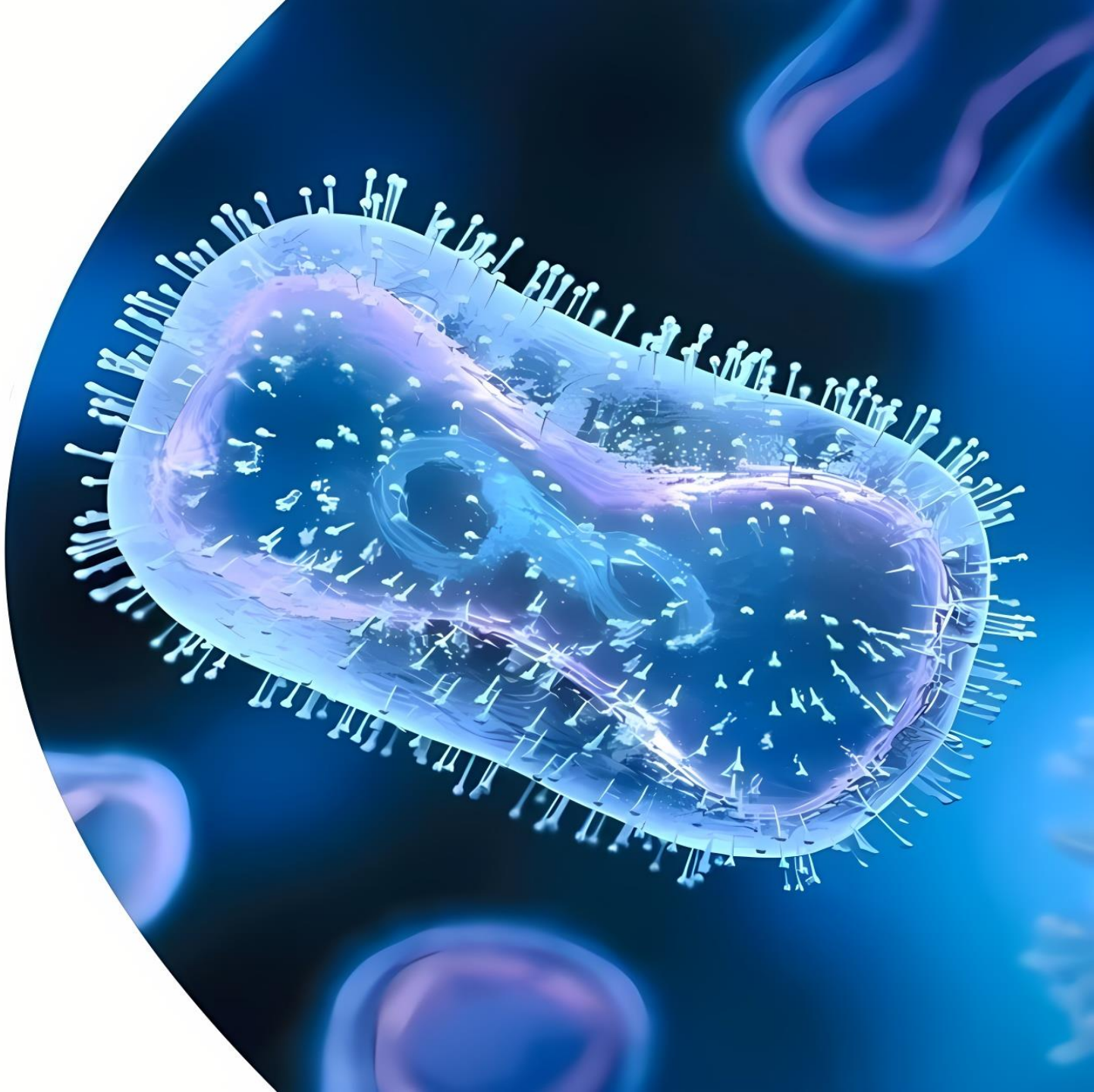
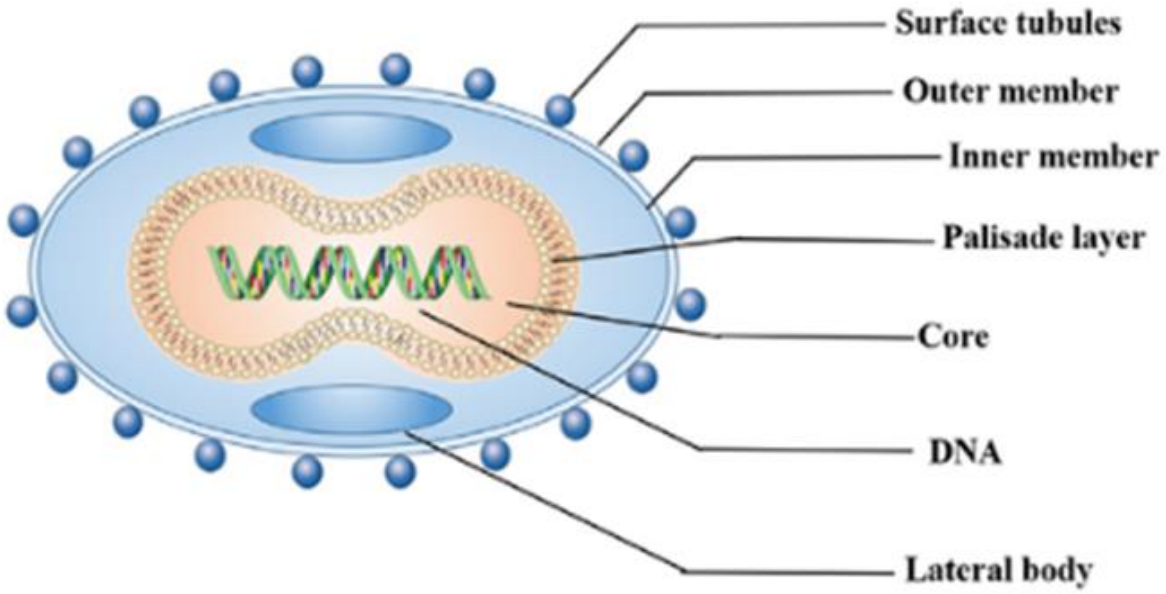
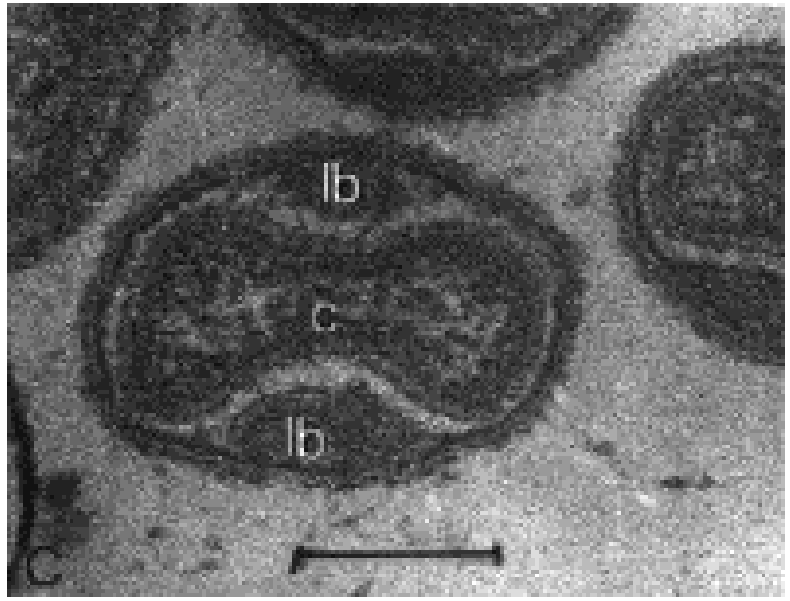
MONKEYPOX VIRUS



MONKEYPOX VIRUS: MPXV

Monkeypox virus (MPXV) is a zoonotic virus belonging to the Orthopoxvirus genus, Poxviridae family.
The Orthopoxvirus genus also includes Vaccinia virus, Cowpox virus, Variola virus and several other animal pathogen poxviruses.



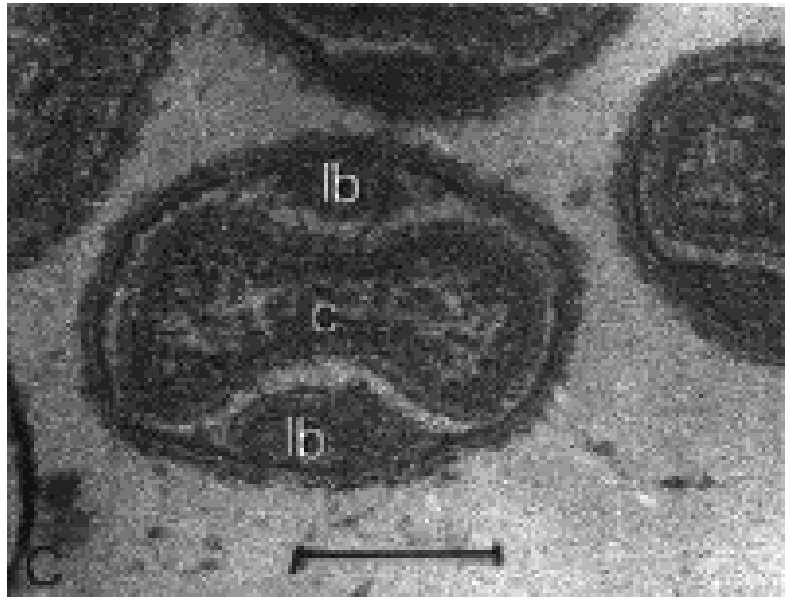


MPXV is an enveloped virus with a dsDNA genome approximately 197 kilobases in length, 200 to 250 nm large, brickshaped, it binds to glycosaminoglycans to enter the host cells, and replicates in the cytoplasm where a hierarchical transcription of early, intermediate, and late genes has been previously described for Orthopoxviruses.

MONKEYPOX VIRUS: MPXV

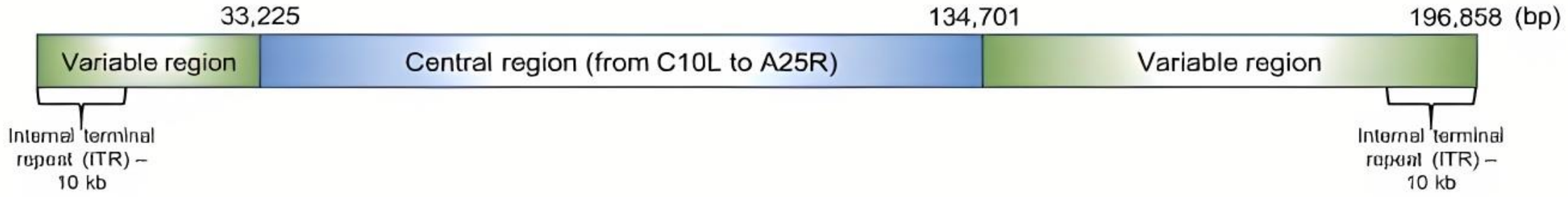
The MPXV virions are brick or ovoid-shaped particles measuring about 200–250 nm and surrounded by a geometrically corrugated lipoprotein outer membrane.

The mature viral particle is composed of several morphologically distinct structural components, including an outer membrane, surface tubules, two lateral bodies, a large double-stranded linear DNA genome (dsDNA), and a double-concave dumb bell-shaped nucleoprotein core



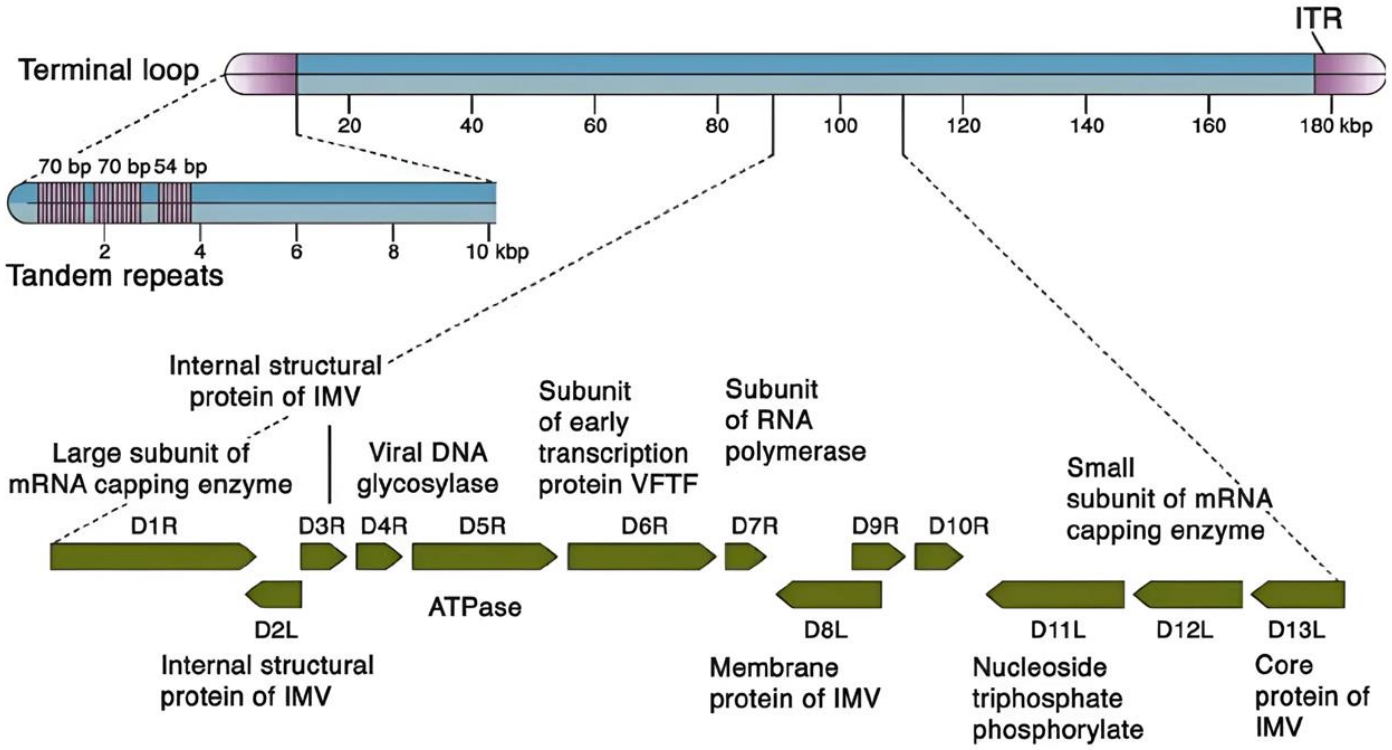
MONKEYPOX VIRUS: GENOME

The genome of the MPXV is about 197.2 kb in length, has covalently closed hairpin ends, and contains over 190 ORFs, encoding for ~180 proteins which play diverse roles in the viral life cycle, including replication, assembly, and modulation of host immune responses



The genome includes a highly conserved central region, encoding for viral transcription, replication, and virion morphogenesis factors, and two peripheral regions containing immune modulating and virulence genes implicated in the determination of the host range and pathogenesis

MONKEYPOX VIRUS: GENOME



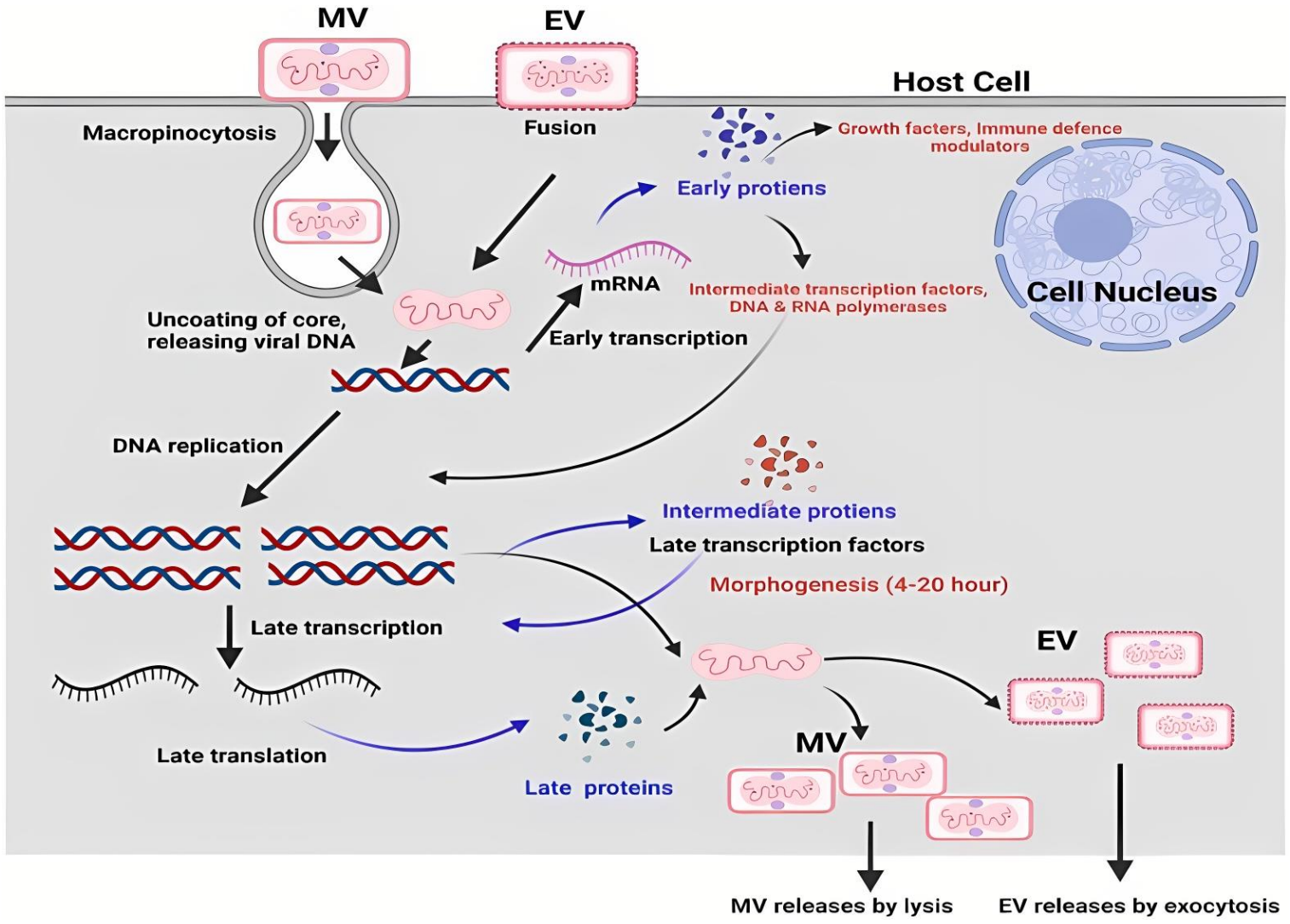
The gene naming was initially based on the HindIII restriction enzyme digestion profiles then on a unified nomenclature for OPXV genes which has been necessary to avoid misinterpretation caused by different reference genomes

Christopher J. et al., 2017

MONKEYPOX VIRUS: LIFE CYCLE

1. ATTACHMENT

The specific receptors for MPXV entry are still unknown, despite it has been proposed that viral entry is associated with host cell type and viral clades, involving multiple surface receptors, such as heparan sulfate, glycosaminoglycans, and chondroitin sulfate

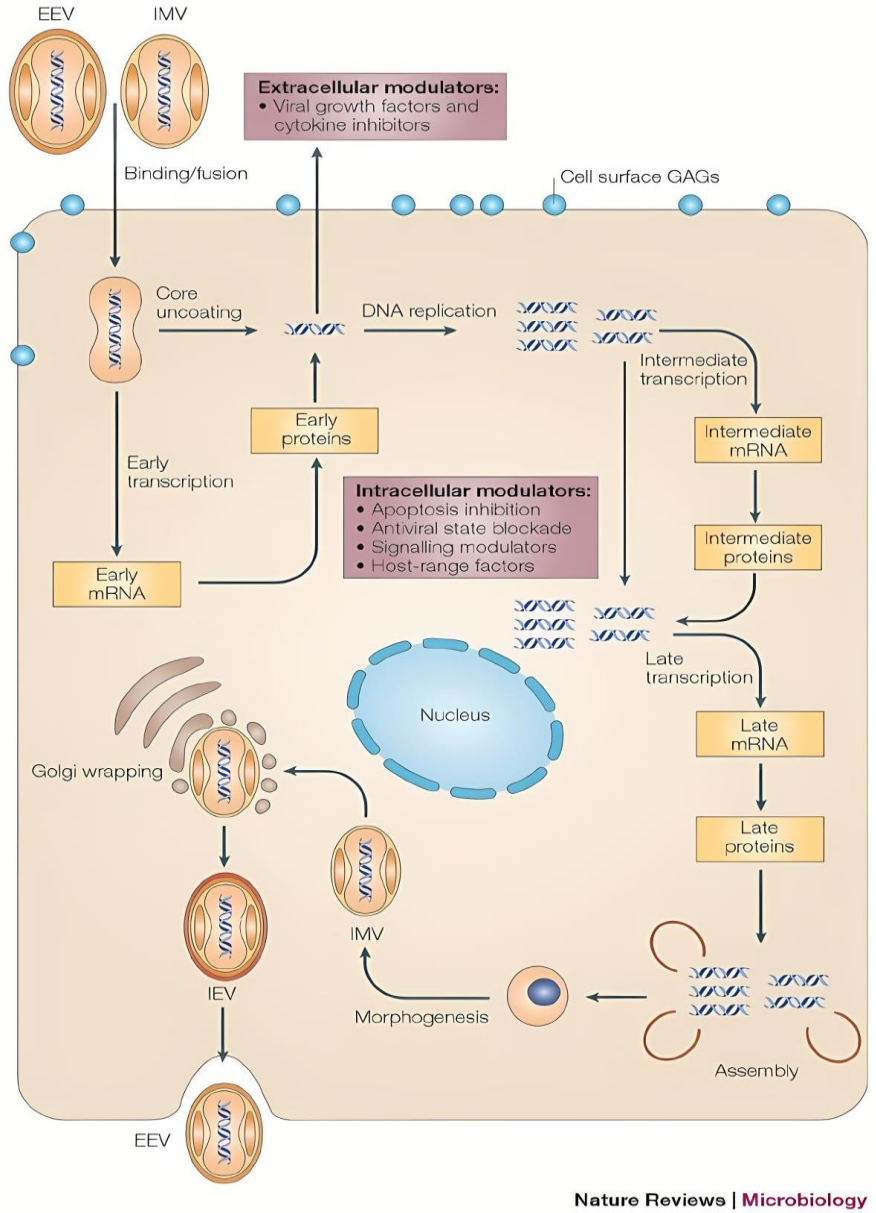


2. ENTRY

the virions enter host cells via direct fusion with the plasma membrane at neutral pH or by a low pH macropinocytosis pathway, releasing the viral core into the cytoplasm

3. UNCOATING AND EARLY GENES EXPRESSION

During the uncoating phase, the viral core is released into the cytoplasm, and viral DNA is transcribed by the MPXV-encoded multi-subunit DNA-dependent RNA polymerases (RNAPs). a complete early transcription system is present within the core of virus particles, providing a mechanism for the synthesis of viral early mRNAs soon after infection. The early mRNAs encode enzymes and factors needed for synthesisof viral DNA and for transcription of the intermediate class of genes and control of the host immunological response.



McFadden G. *Poxvirus tropism*. Nat Rev Microbiol. 2005 Mar;3(3):201-13. doi: 10.1038/nrmicro1099. PMID: 15738948; PMCID: PMC4382915

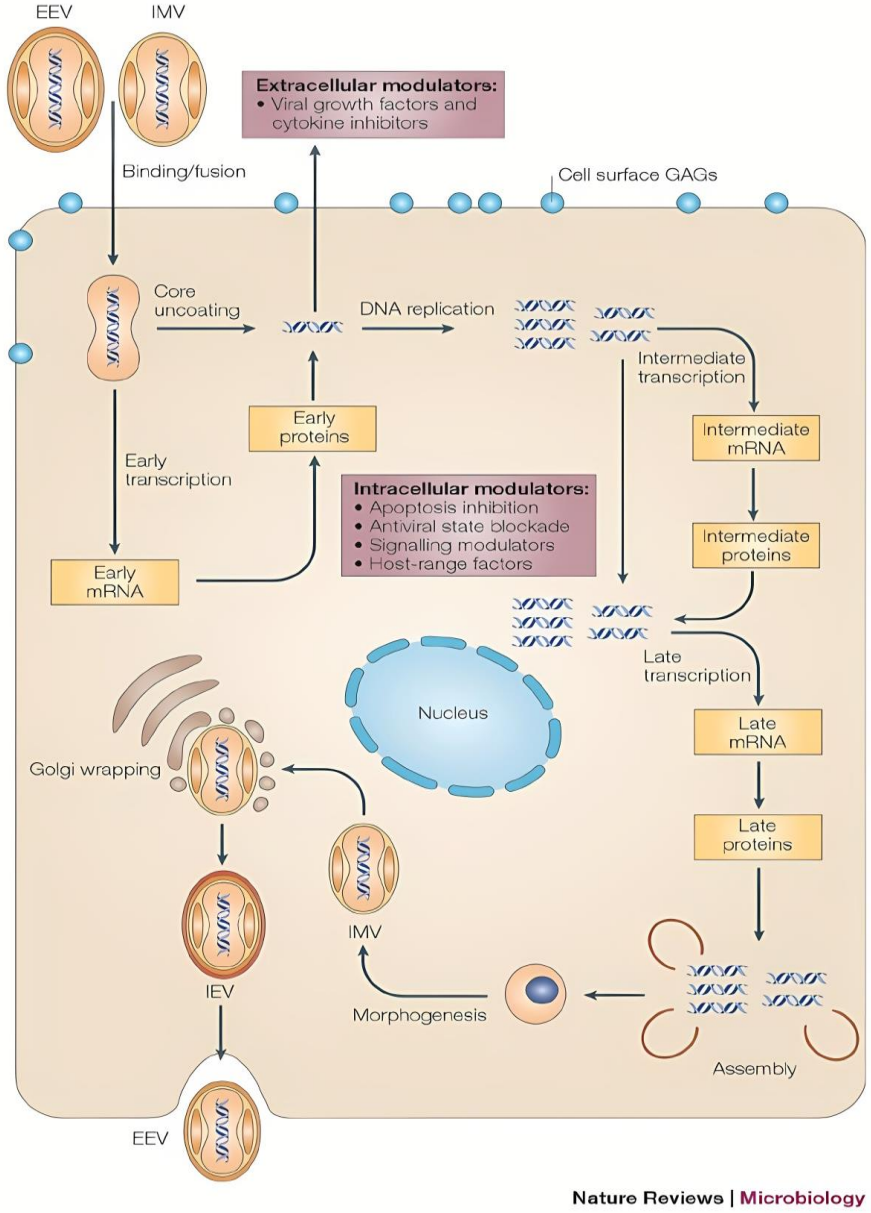
4. DNA REPLICATION

In the DNA replication phase, the viral DNA polymerase replicates the viral genome.

5. INTERMEDIATE AND LATE GENES EXPRESSION

Intermediate and late gene expression occurs, creating structural proteins and enzymes necessary for virion assembly. Early factors to include in the virion are also produced

the intermediate gene transcripts encode enzymes and factors for late gene expression; and the products of the late genes include the early transcription factors, which are packaged with RNA polymerase and other enzymes in progeny virions

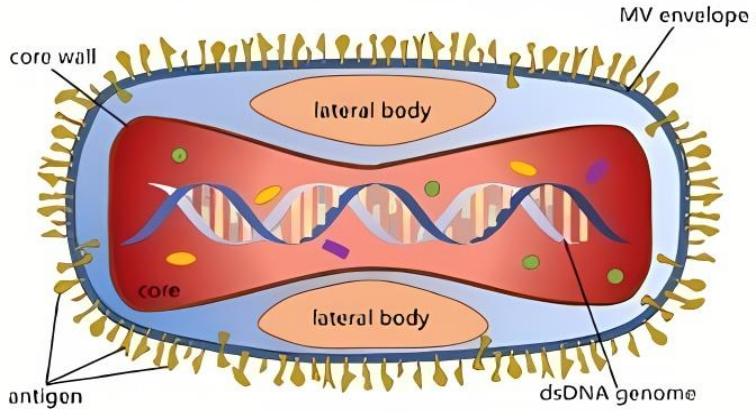


McFadden G. *Poxvirus tropism*. Nat Rev Microbiol. 2005 Mar;3(3):201-13. doi: 10.1038/nrmicro1099. PMID: 15738948; PMCID: PMC4382915

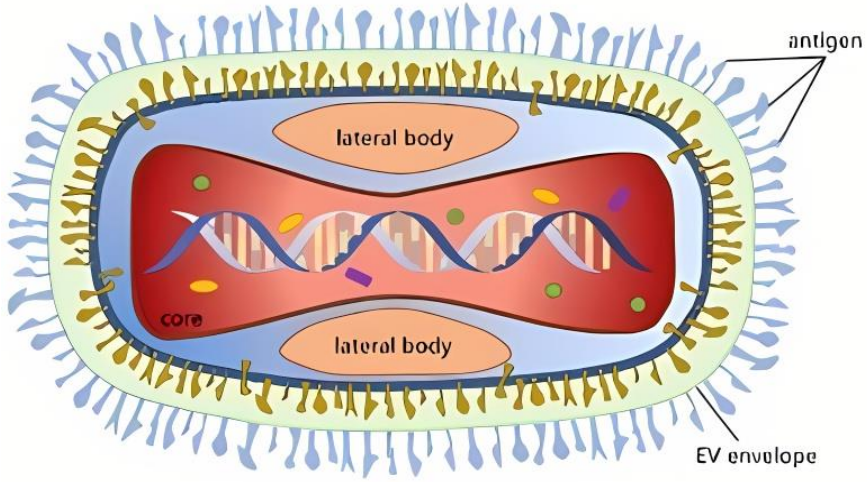
6. ASSEMBLY AND MORPHOGENESIS

MPXV produces two morphologically distinct infectious forms: extracellular enveloped virus (EEV), which is thought to be responsible for early dissemination, and intracellular mature virus (IMV), which is released during cell lysis.

EEV and IMV particles have a different number of surface glycoproteins and enveloping membranes.
The late proteins assemble into infectious virion IMVs. Some IMVs are transported through microtubules and wrapped by a double membrane derived from the endoplasmic reticulum or Golgi to produce an intracellular enveloped virus (IEV). These enveloped virions can further fuse with the cell membrane via triggering actin polymerization and be released to form EEVs



Mature Virion (MV)



Enveloped Virion (EV)

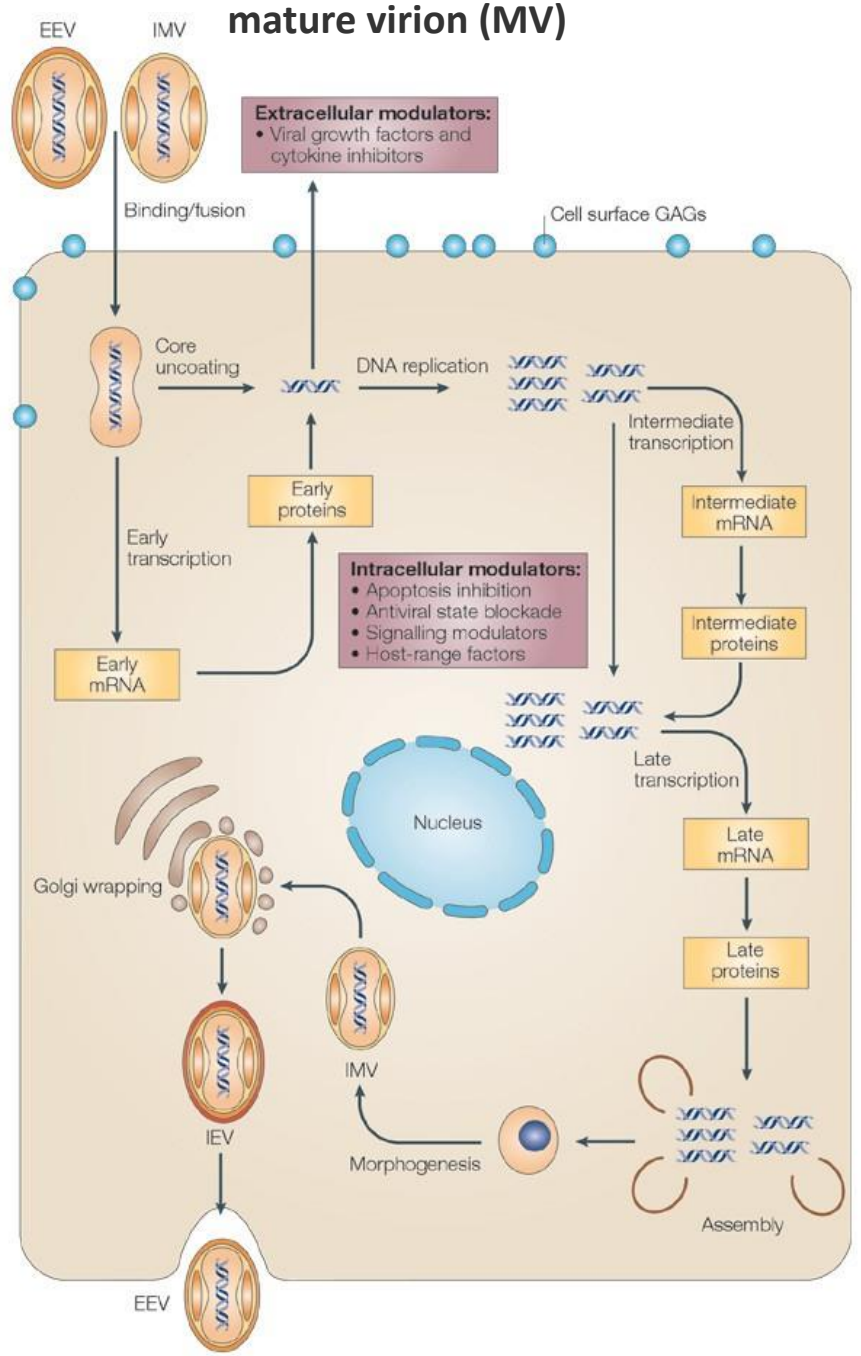
https://www.researchgate.net/figure/Schematic-diagram-of-monkeypox-virus-MPXV-structure-A-The-structure-of-intracellular_fig1_365249837

7. RELEASE

Two infectious viral particles are produced: the mature intracellular virions (MV) which exit through lysis and the extracellular enveloped virions (EV) which exit by exocytosis

MV and EV differ in their surface glycoproteins and the number of surrounding membranes. The EV form has an additional lipid membrane.

The two viral forms enter cells through different mechanisms: EV via fusion, MV via macropinocytosis.



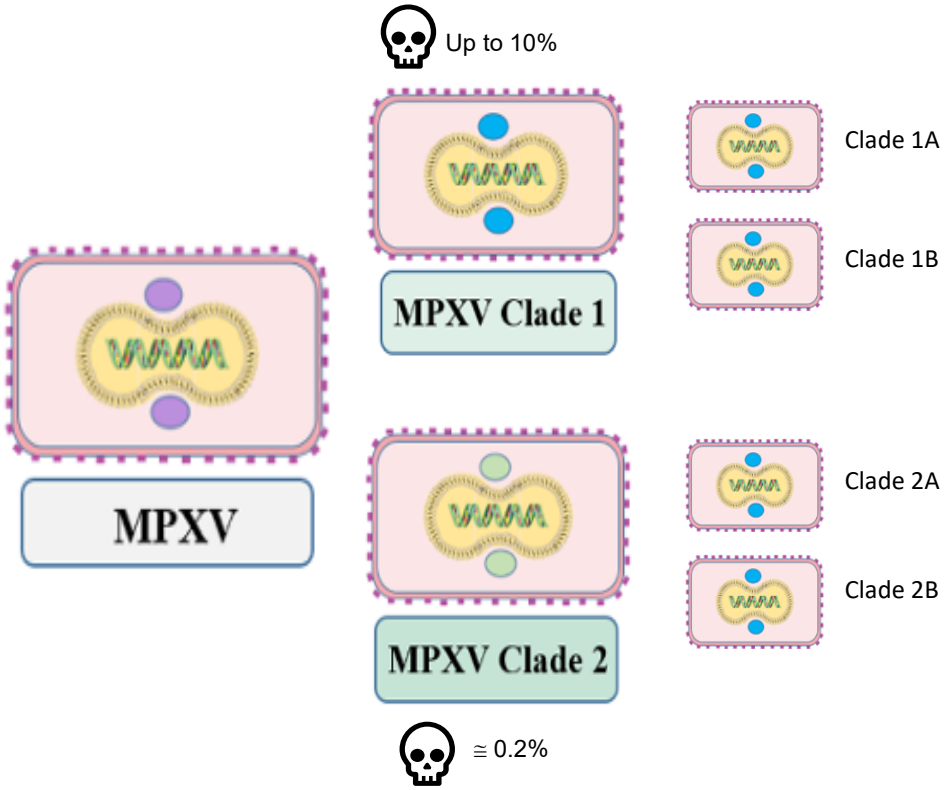
McFadden, G. Poxvirus tropism. *Nat Rev Microbiol* **3**, 201–213 (2005). https://doi.org/10.1038/nrmicro1099

MONKEYPOX VIRUS: TAXONOMY

- Family: **Poxviridae**
- Genus: **Orthopoxvirus**

MPXV is subdivided into two major clades: Clade I which is subdivided in subclades Ia and Ib, with higher virulence and an average mortality rate of up to 10%; and Clade II which includes subclades IIa and IIb, the latter responsible for the global 2022 outbreak, which has a mortality rate of 0,2%

Formerly Congo Basin or Central Africa

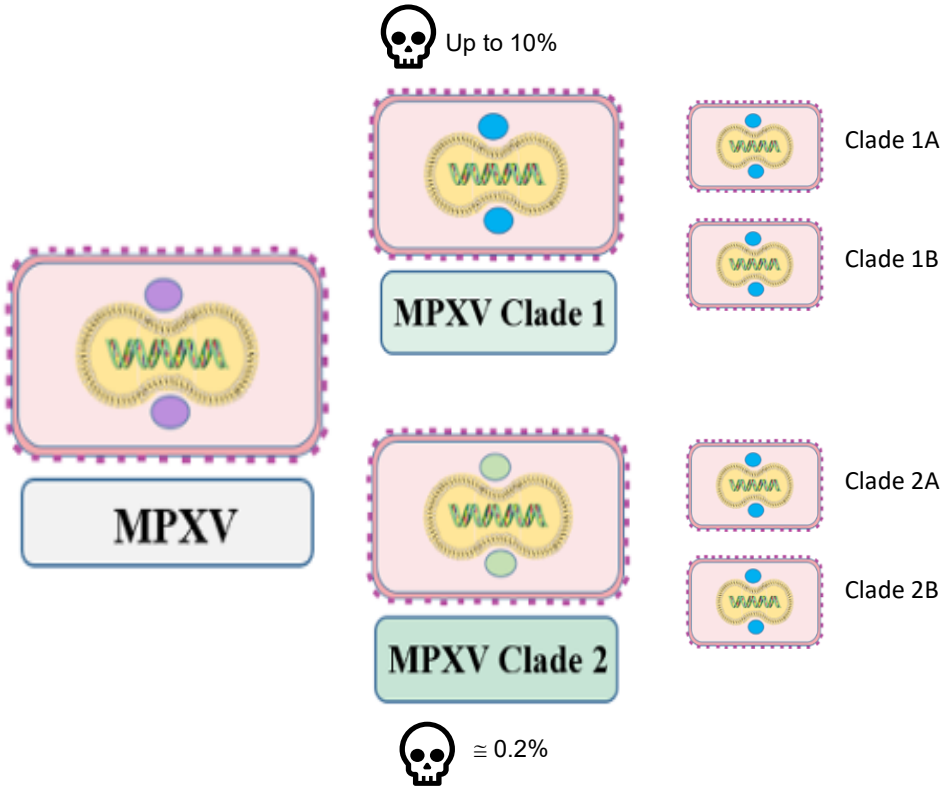


Formerly West Africa

MONKEYPOX VIRUS: TAXONOMY

Clade Ia MPXV circulates within multiple countries in Central Africa and is associated with regular spillover from animal reservoirs with some onward human-to-human transmission.

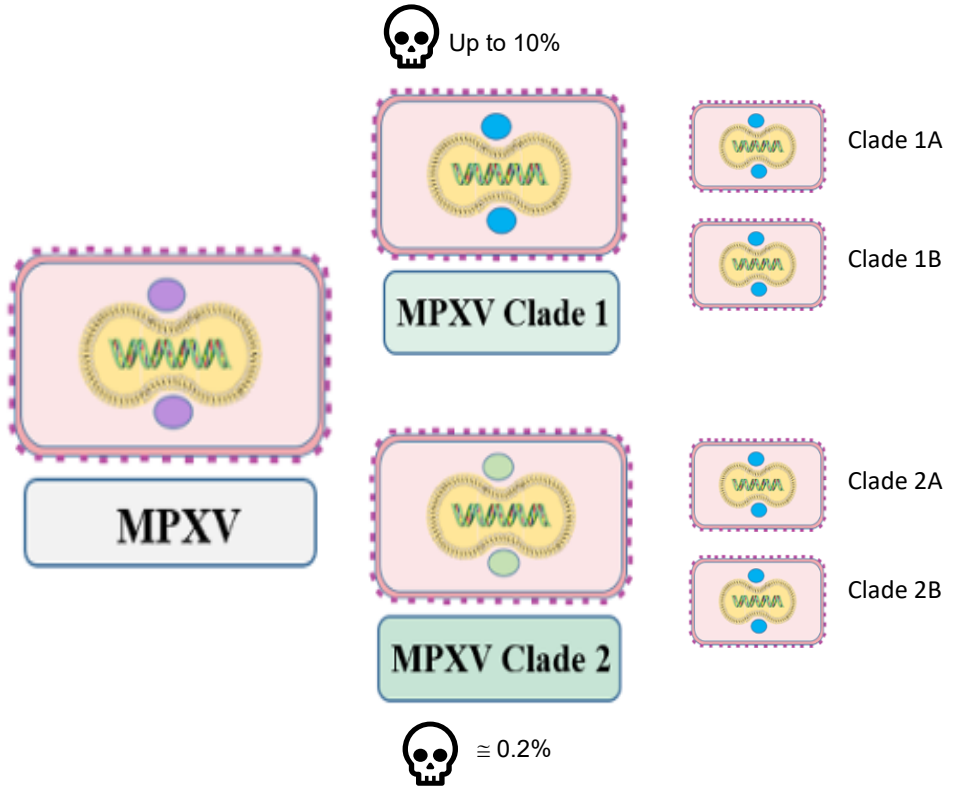
Clade Ib MPXV recently emerged in the eastern part of the Democratic Republic of the Congo and is undergoing sustained human-to-human transmission (CDC 2025).



MONKEYPOX VIRUS: TAXONOMY

Clade IIa MPXV has historically rarely been isolated and documented in humans with most available genetic sequences coming from animal species, and more recent transmission in several West African countries in bordering countries and outside Africa

Clade IIb MPXV, 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 (CDC 2025).



MONKEYPOX VIRUS: CLADES

- A genomic comparison of MPXV clades indicates similar gene synteny, but there are differences in gene content among the clades due to some genes that are missing or truncated in either one or two clades (Alakunle et al. 2024).
- Clades I and II differ by approximately 0.55% to 0.56% in their genomic nucleotide sequences, indicating that they evolved from a common ancestor some centuries ago. The genetic difference between subclades IIa and IIb is less pronounced, indicating their closer evolutionary link within clade II (Jumar S. et al. 2025).
- In clade II several genes involved in immune modulation or virulence are either missing or truncated, including the OPG032, coding for the complement control protein.

One characteristic feature of the MPXV clade II compared to clade I is the absence of the viral complement control protein CCP or MOPICE (OPG032) concurring with the attenuated pathogenicity observed for this clade

OPEN ACCESS Freely available online

PLOS one

Elucidating the Role of the Complement Control Protein in Monkeypox Pathogenicity

2012

Paul N. Hudson[1]*, Joshua Self[1], Sonja Weiss[1], Zachary Braden[1], Yuhong Xiao[2], Natasha M. Girgis[2], Ginny Emerson[1], Christine Hughes[1], Scott A. Sammons[1], Stuart N. Isaacs[2], Inger K. Damon[1], Victoria A. Olson[1]

Since 2022 we have observed changes in transmission route with the predominant role of human-to-human transmission

nature medicine

Brief Communication

https://doi.org/10.1038/s41591-024-03130-3

Clade Ib

2024

Sustained human outbreak of a new MPXV clade I lineage in eastern Democratic Republic of the Congo

A large ~1 kbp deletion in the OPG032 gene and interfering with the clade I-specific diagnostic PCR originally developed by Li et al. APOBEC editing high

RESEARCH

MPOX

APOBEC3 deaminase editing in mpox virus as evidence for sustained human transmission since at least 2016

Áine O'Toole[1]*, Richard A. Neher[2], Nnaemeka Ndodo[3], Vitor Borges[4], Ben Gannon[5], João Paulo Gomes[4,6], Natalie Groves[7], David J. King[8], Daniel Maloney[1], Philippe Lemey[9], Kuiama Lewandowski[5], Nicholas Loman[7,10], Richard Myers[7], Ifeanyi F. Omah[1,11], Marc A. Suchard[12], Michael Worobey[13], Meera Chand[7,14], Chikwe Ihekweazu[3], David Ulaeto[7]†, Ifedayo Adetifa[3]†, Andrew Rambaut[1]*†

We suggest that the APOBEC3-driven evolution of recent clade IIb MPXV is a signature of a switch to sustained transmission within the human population.

Since 2022 we have observed changes in transmission route with the predominant role of human-to-human transmission

the establishment of subclade IIb, is worrying because of its increased transmissibility. Genomic studies revealed that strains of this subclade had a greater number of single-nucleotide polymorphisms (SNPs), indicating a faster rate of evolution, than did previous strains. Subclades IIa and IIb differ principally in terms of epidemiological patterns and genetic makeup; subclade IIb has demonstrated a greater propensity for human-to-human transmission during epidemics, whereas subclade IIa remains more confined

RESEARCH

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Since 2022 we have observed changes in transmission route with the predominant role of human-to-human transmission

Clade Ib and Clade IIb MPXV lineages have extensive APOBEC3 editing signatures across their genome, which have occurred over many years.

Science

Historically, mpox has been characterized as an endemic zoonotic disease that transmits through contact with the reservoir rodent host in West and Central Africa. However, in May 2022, human cases of mpox were detected spreading internationally.

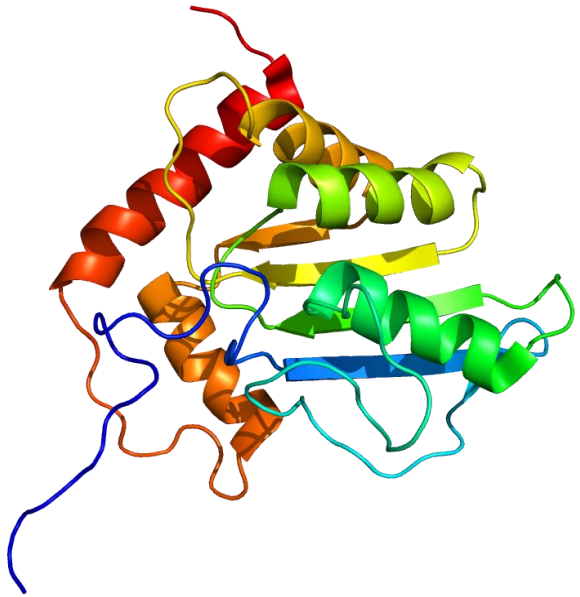
We developed a dual-process phylogenetic molecular clock that—inferring a rate of ~6 APOBEC3 mutations per year—estimates that MPXV has been circulating in humans since 2016.

These observations of sustained MPXV transmission present a fundamental shift to the perceived paradigm of MPXV epidemiology as a zoonosis

APOBEC3 is a cytosolic mRNA editing enzyme that has been shown to induce C-to-T and G-to-A mutations in DNA viruses including MPXV

APOBEC: proteina antivirale o proteina pro virale?

- Questa proteina è una citosina deaminasi che immette degli errori nel codice genetico dei retrovirus

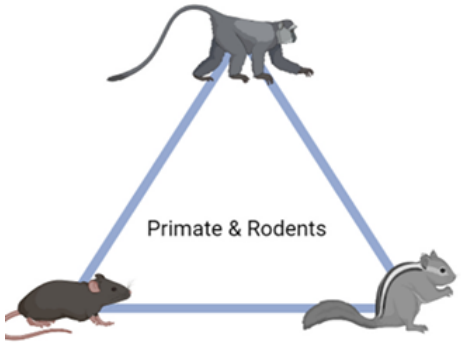


APOBEC3G

- ...è possibile che l'apporto mutazionale garantito da queste citosine deaminasi procuri in Monkeypox benefici e vantaggi!

TRANSMISSION OF MPXV

Animal-to-animal

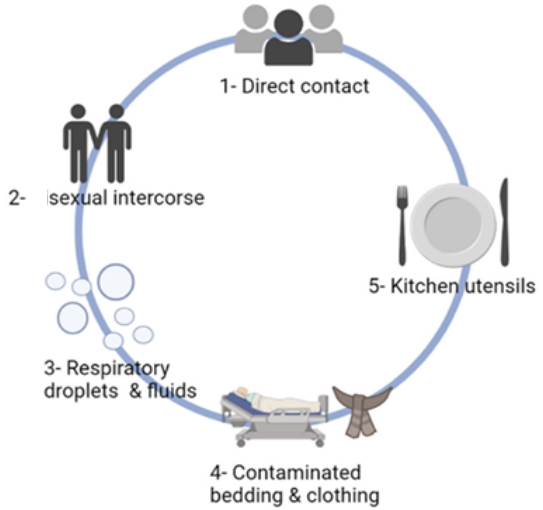


Animal-to-human

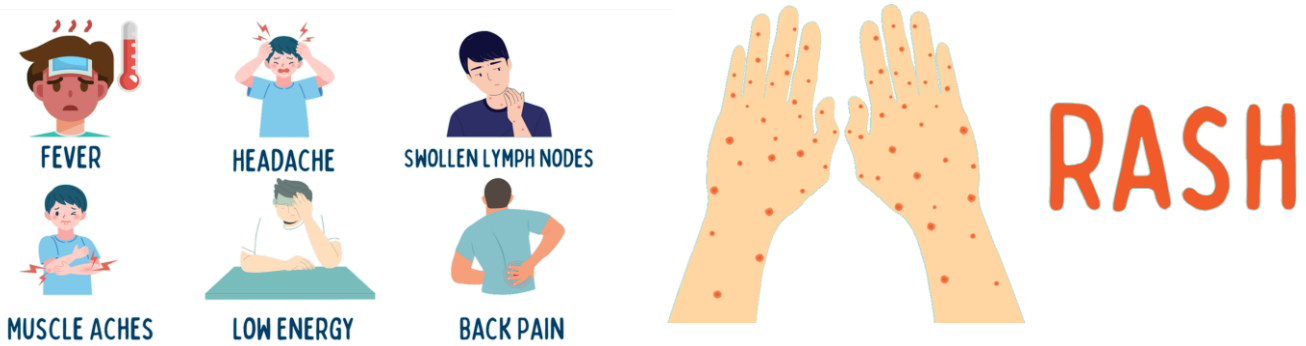
1- Direct contact with animals
2- Animal bite
3- Animal scratch
4- Raw meat consumption

Horizontal transmission

Human-to-human



SYMPTOMS OF MPOX



PEOPLE AT HIGH RISK

Immunocompromised individuals

Children

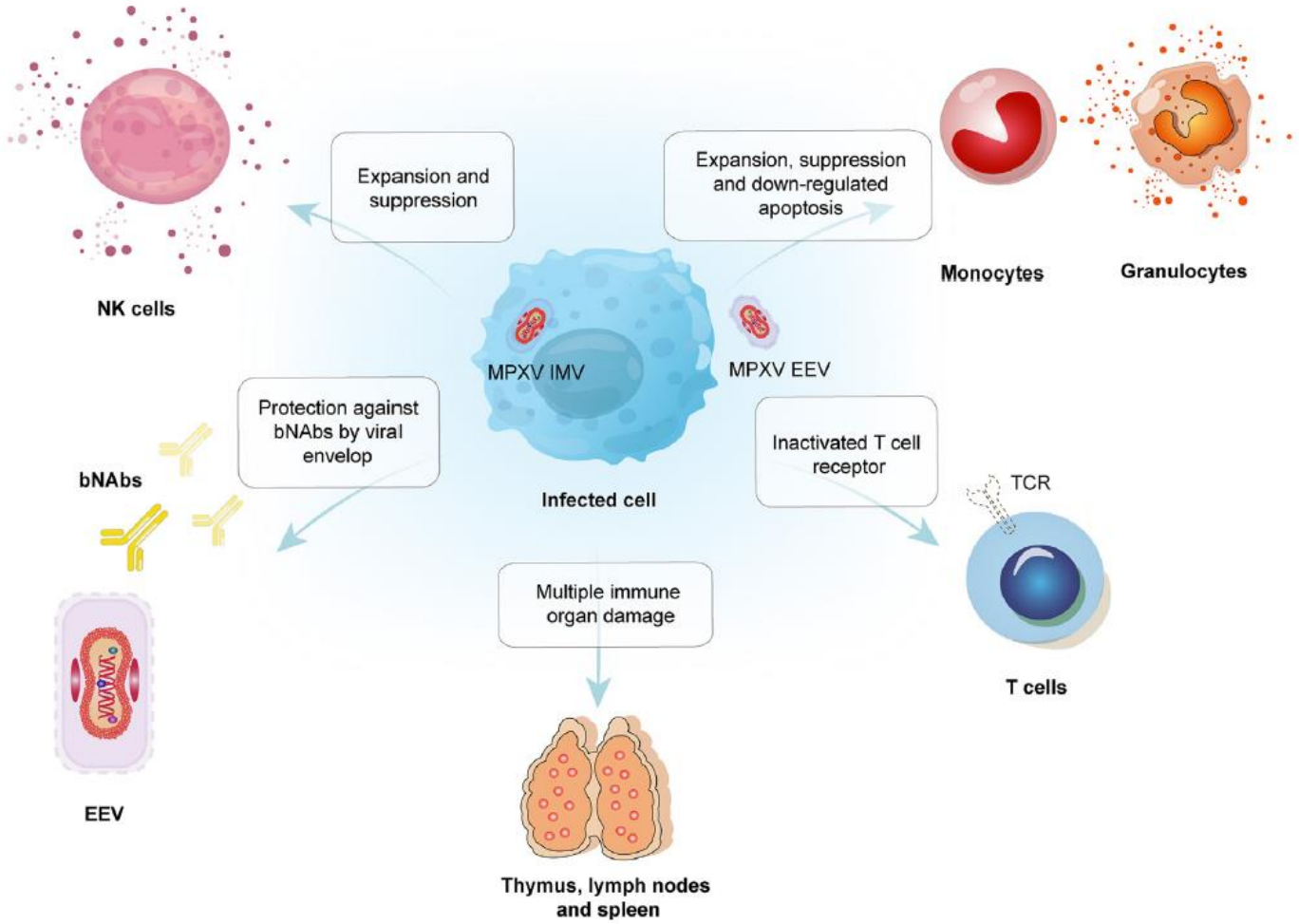
Pregnant women

Karagoz, Aysel, et al. "Monkeypox (mpox) virus: Classification, origin, transmission, genome organization, antiviral drugs, and molecular diagnosis." Journal of infection and public health (2023).
Falendysz, E. A. et al. Monkeypox virus in animals: current knowledge of viral transmission and pathogenesis in wild animal reservoirs and captive animal models. Viruses, (2023)

MPXV: tropism

- MPXV enters the body by the mucosal or cutaneous route, infecting mucosal epithelial cells or keratinocytes, dermal fibroblasts and endothelial cells, establishing a productive, cytopathic infection (Cann J. A. et al. 2023; Yael Hammerschlag et al. 2022).
- After the development of a primary viremia resulting from infection of lymphoid tissues, the virus can spread to distant organs (Chapman J. L. et al. 2010), the spleen and liver representing the main target organs; infection in these organs results in a second viremia leading to viral spread to the lungs, kidneys, intestines, skin, and gonads

MPXV: tropism



Central role for NK cells,
T cell and Humoral response via neutralizing Ab

Infection of monocytes/macrophages

Fig. 1. The immune response following MPXV infection and the immune evasion strategies employed by MPXV. Briefly, MPXV triggers widespread expansion of both innate and adaptive immune cells. In the initial stages post-infection, the proliferation of monocytes, granulocytes, and NK cells is significantly increased. Moreover, MPXV employs multiple strategies to evade the host immune response. It suppresses the activation of monocytes, granulocytes, and natural killer (NK) cells, inhibiting their apoptosis and allowing them to be used as vectors for their spread. Additionally, MPXV can inactivate the TCR on $CD4^+$ and $CD8^+$ T cells, hindering their activation. Furthermore, it integrates host-cell membrane proteins to shield itself from neutralizing antibodies. This process also causes damage to multiple immune organs. MPXV: Mpox virus; NK cells: natural killer cells; IMV, intracellular mature virion; EEV: extracellular enveloped virion; TCR: T-cell receptor; bNAbs: broadly neutralizing antibodies.

MPXV: evasion from the Immune response

	Clade I Mpox virus	Clade II Mpox virus
Blood Monocyte	Increased proliferation and reduced apoptosis	Increased proliferation
Natural killer cell	Significant expansion and suppressed IFN production	Significant expansion and suppressed IFN production
cGAS-STING NF-κB pathway	Mimicking NF-κB p65 subunit with F14 protein	Mimicking NF-κB p65 subunit with F14 protein
Caspase-1	Inhibition with SPI-2 and CrmA	Inhibition with SPI-2 and CrmA
DNA-PK	Binding to Ku heterodimer with C16 protein	Binding to Ku heterodimer with C16 protein
IFN-PKR pathway	Suppressing PKR with F3 protein with truncated N-terminal but absent of K3 protein	Suppressing PKR with F3 protein with truncated N-terminal but absent of K3 protein
Complement system	Blocking C3 and C4 component interaction with MOPICE	Absence of MOPICE
Cell-mediated immunity	Interfere with T cell control using the B22 protein, interrupt CD28 signaling with the M2 protein, and induce nonresponse of the TCR	Interfere with T cell control using the B22 protein, interrupt CD28 signaling with the M2 protein, and induce nonresponse of the TCR

Fig 4. Regulation of immune components among clade I and II of Mpox (Fang D. et al. 2024).

MPXV: evasion from Immune response

Two caspase-1 inhibitory proteins and a PKR escape-related protein have been identified as phylogenomic hubs involved in modulating the immune environment during the MPXV infection.

With respect to adaptive immunity, MPXV exhibits unique and exceptional T-cell inhibition capabilities, thereby comprehensively remodeling the host immune environment.

The viral envelope also poses challenges for the neutralizing effects of antibodies and the complement system

MPXV: evasion from DNA sensing

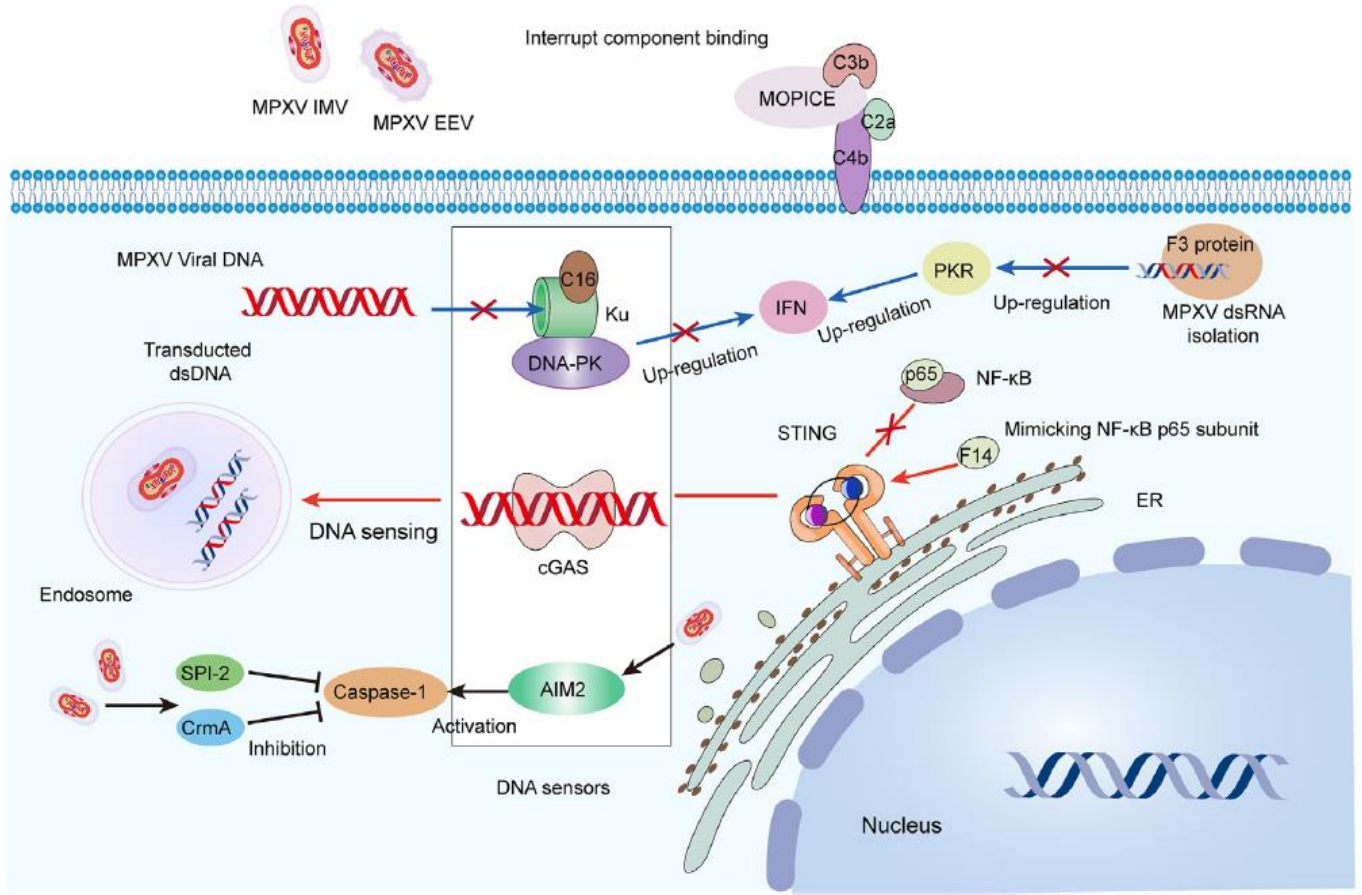


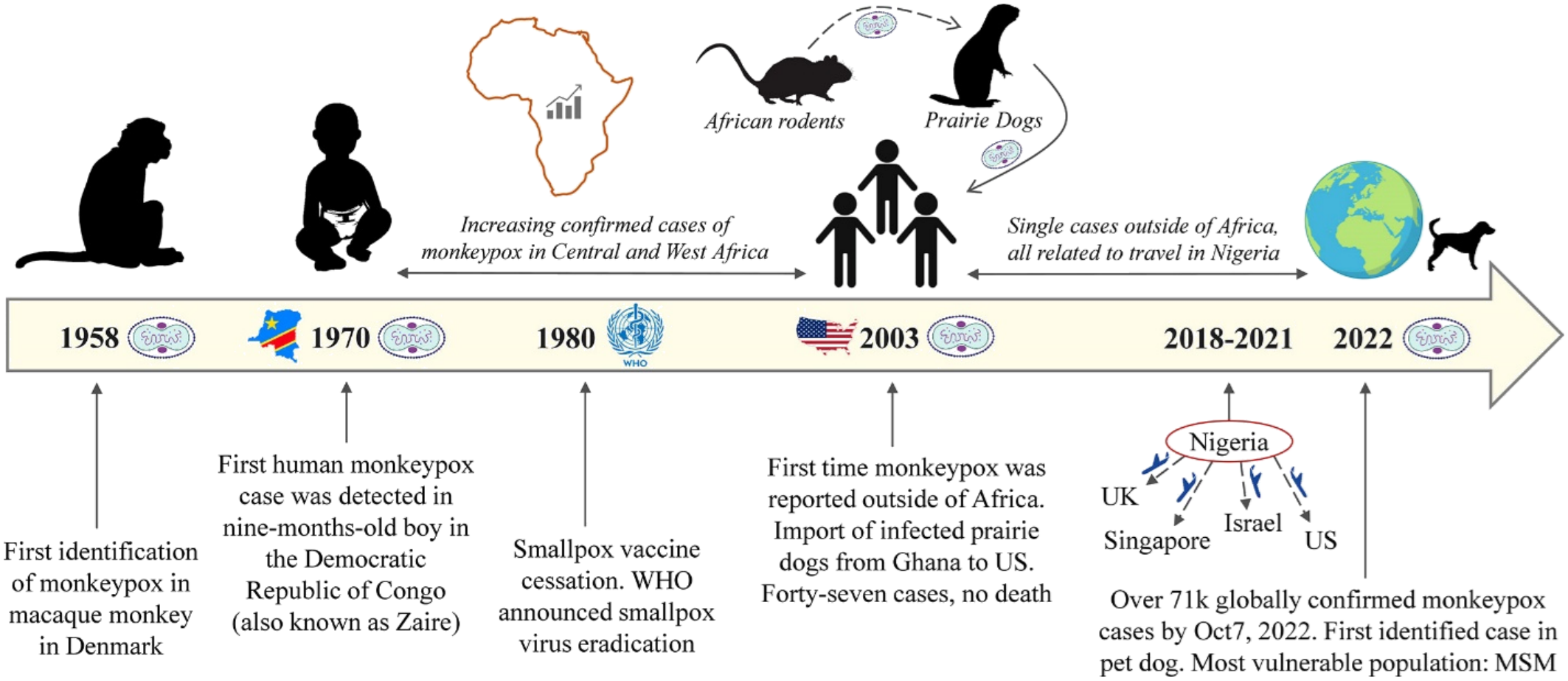
Fig. 2. Immune evasion of DNA sensors and complements by MPXV. MPXV specializes in evading DNA sensing and complement responses. It induces the rapid decay of C3 convertase and encodes MOPICE to prevent the binding of the third and fourth components, disrupting both the classical and alternative complement pathways. Poxviruses produce C4 and/or C16 protein (MPXV only produces C16) which bind to Ku heterodimer, preventing it from recognizing viral genome, recruiting protein kinase catalytic domain and up-regulating IFN; MPXV produces F14 protein to mimic the p65 subunit of NF-κB and inhibits selectively the activation of NF-κB-dependent antiviral genes thus interrupting cGAS-STING pathway; MPXV produces SPI-2 and CrmA to inhibit caspase-1 activation and abolishes IFN-β induction thus suppressing apoptosis; MPXV produces F3 protein to bind viral dsRNA and isolates it from PKR to prevent IFN up-regulation. MPXV: Mpox virus; MOPICE: MPOX inhibitor of complement enzyme; dsDNA/RNA: double-strand DNA/RNA; DNA-PK: DNA-dependent protein kinase; PKR: protein kinase R; cGAS: cyclic GMP-AMP synthase; STING: Stimulator of interferon genes; ER: Endoplasmic reticulum; SPI-2: Poxvirus serine proteinase inhibitor 2; CrmA: cytokine response modifier A.

MPXV: evasion from Immune response

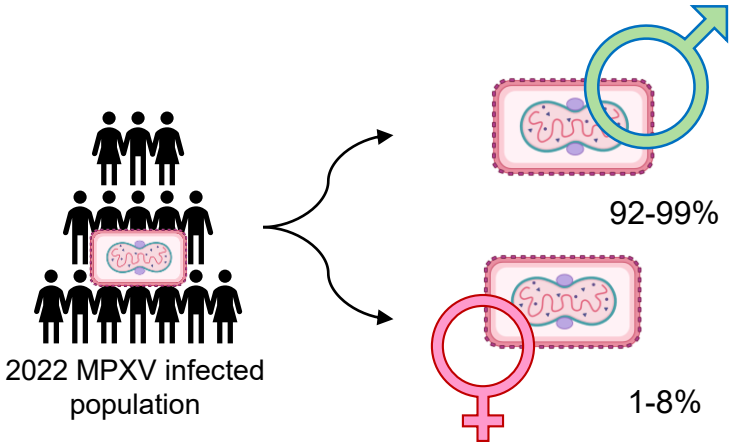
MPXV also secretes soluble decoy receptors that bind and neutralize interferons and pro-inflammatory cytokines (e.g., TNF-α, IL-1β), thereby suppressing early immune responses and facilitating viral replication

Infected cells can block both $CD4^+$ and $CD8^+$ T cell responses through mechanisms that do not depend on MHC class I downregulation. Instead, MPXV directly inhibits T cell receptor (TCR) signaling, preventing cytokine production and cytotoxic activity.
This immune evasion enables MPXV to persist in host tissues and may contribute to asymptomatic transmission and prolonged viral shedding

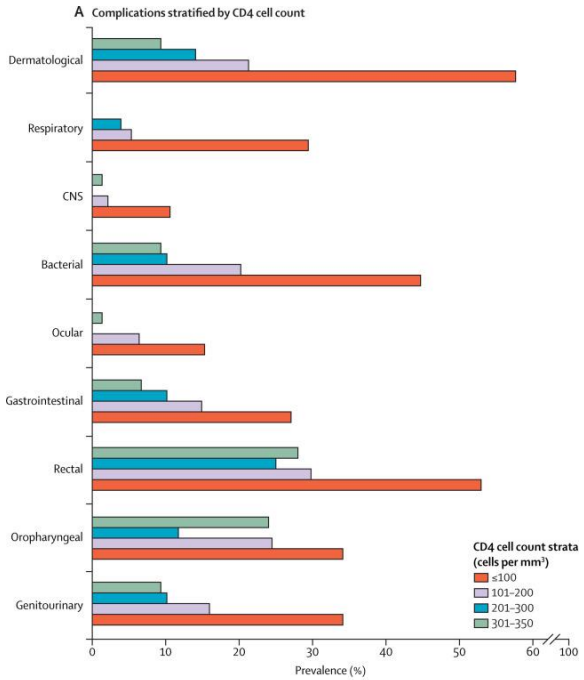
Mpox: a neglected tropical disease goes global

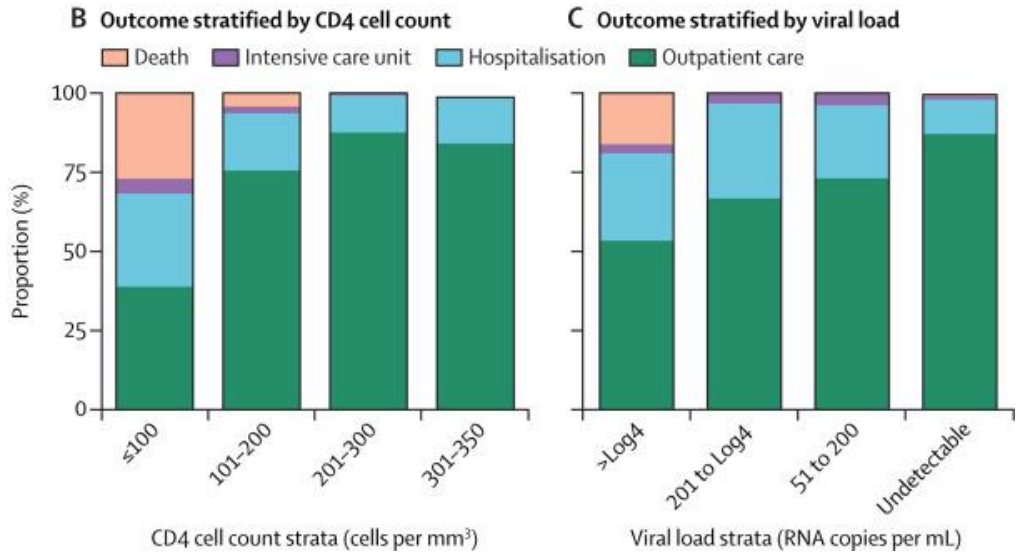


Mpox: a sexually transmitted disease



In 2022
Sexual transmission
=
Preferential route of infection
(men and women)



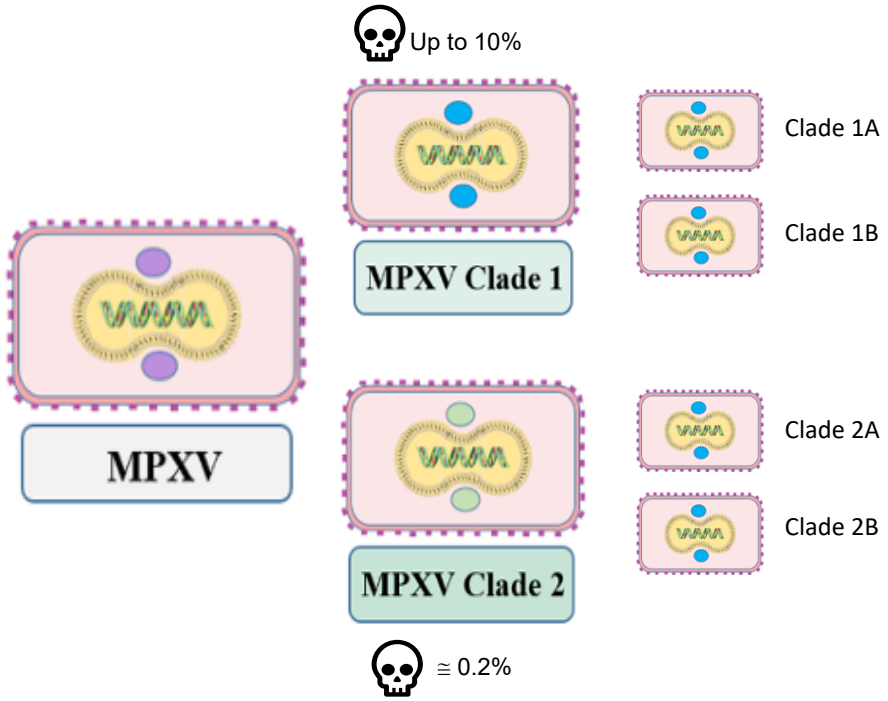


PEOPLE AT HIGH RISK

PLWH CD4+T <350 cells/mm3

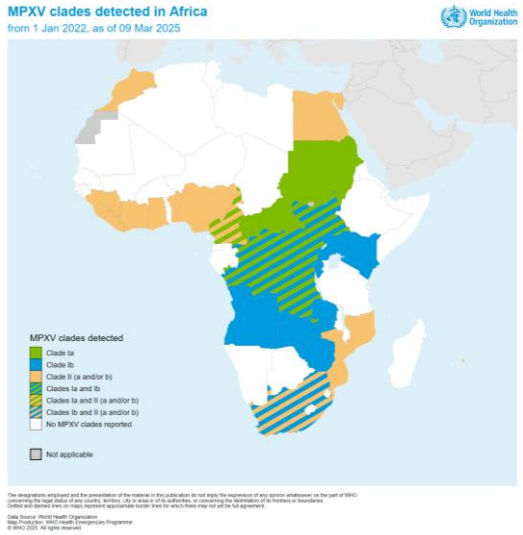
Images created with BioRender.com

Since May 2022, global spread of clade IIb, then, on August 2024, the WHO declared the public health emergency of international concern given the increase in mpox cases in the Democratic Republic of Congo (DRC) and its expansion to neighbouring countries. Co-circulation of Clade Ia, Ib, IIa, IIb



Since 2022 we have observed changes in transmission route with the predominant role of sexual transmission in viral spread.

Year	Total Cases	Total Deaths	Countries reporting cases
2022	84 964	138	109
2023	10 341	45	76
2024	30 508	89	85
2025	3724	11	51



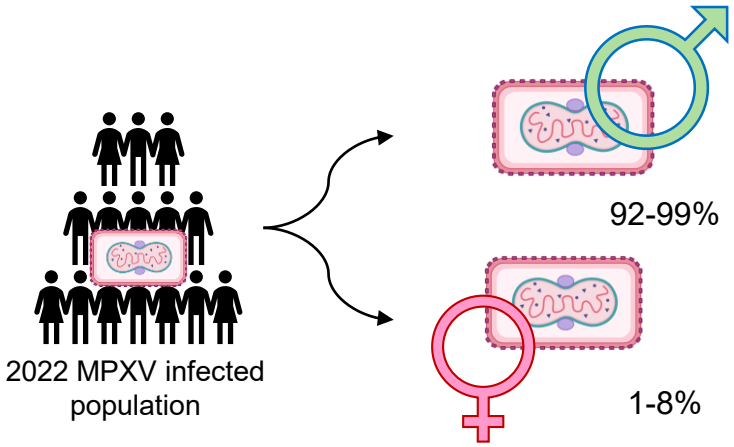
The clade IIb lineage B.1 is characterized by a much higher reproduction number in humans compared to previous strains.

IIb is enriched in APOBEC3 mutations (considered the dominant driver of adaptive microevolution in humans) *vs* IIa

Clade Ia is linked to zoonotic spillovers and clade Ib is characterised by sustained human-to-human sexual transmission.

Clade Ib also shows APOBEC3-driven mutations that enhance viral transmissibility

Mpox: a sexually transmitted disease

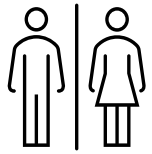


Men who have sex with men (MSM)
85%

In prior epidemics, over 30% of MPOX cases

Since 2022
Sexual transmission
=
Preferential route of infection
(men and women)

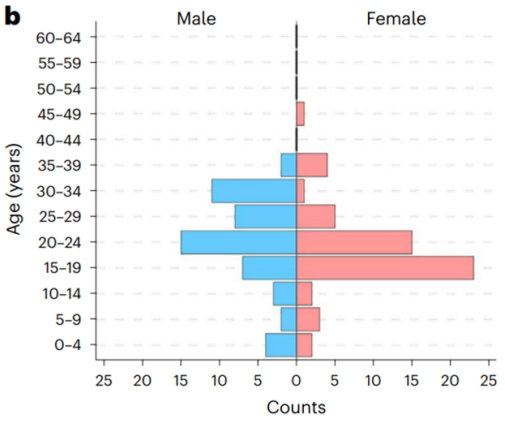
51.9%



29%
sex workers

As with previous epidemics, female individuals are once again becoming widely involved

Sexual transmission confirmed as the main route of transmission



Images created with BioRender.com

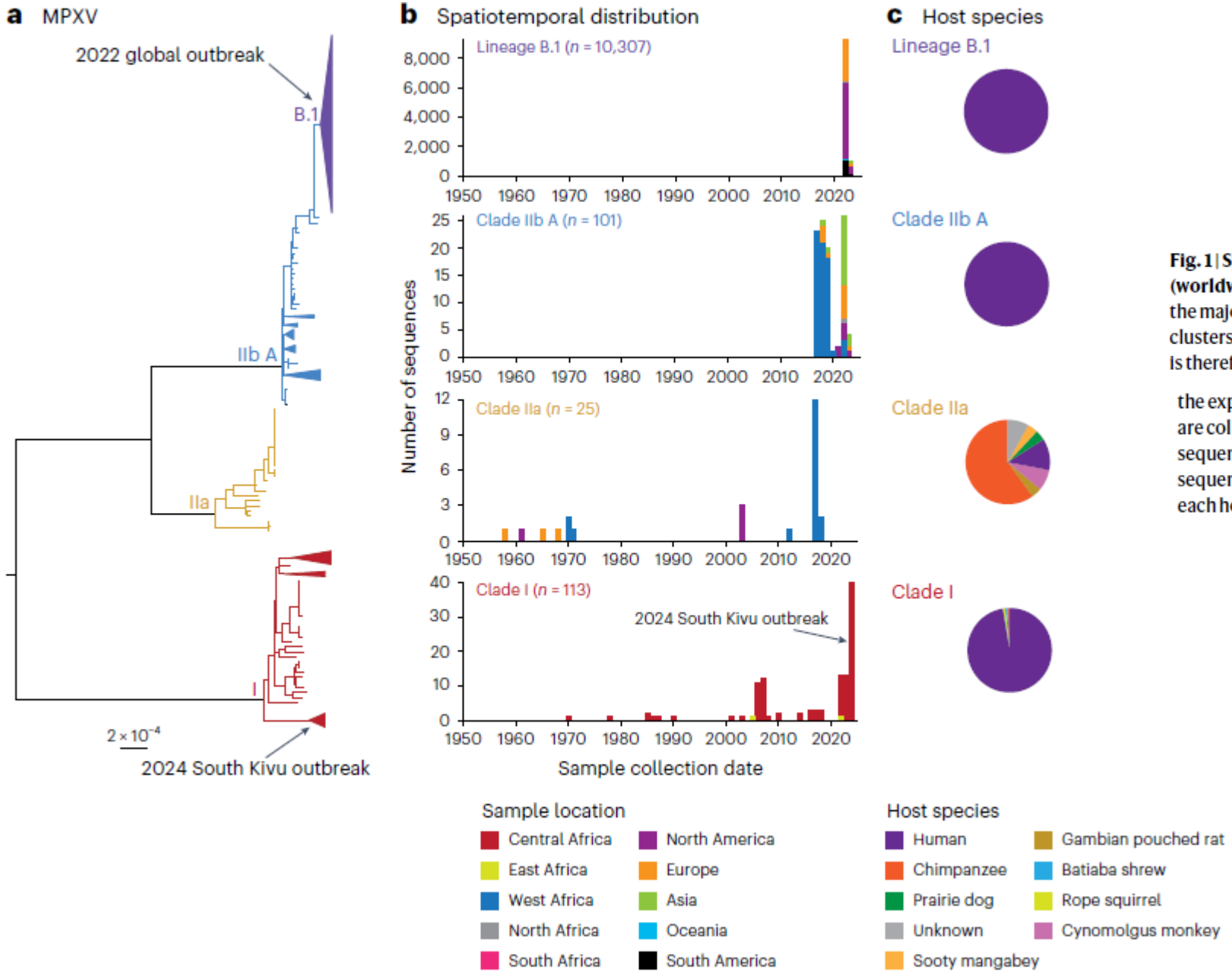
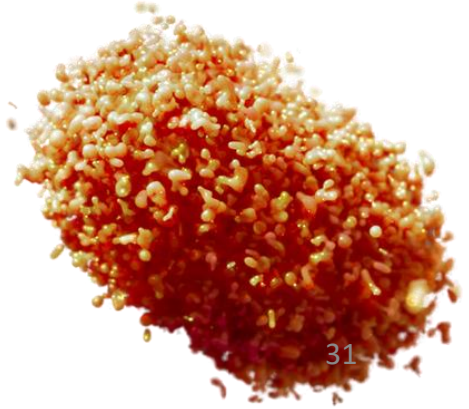


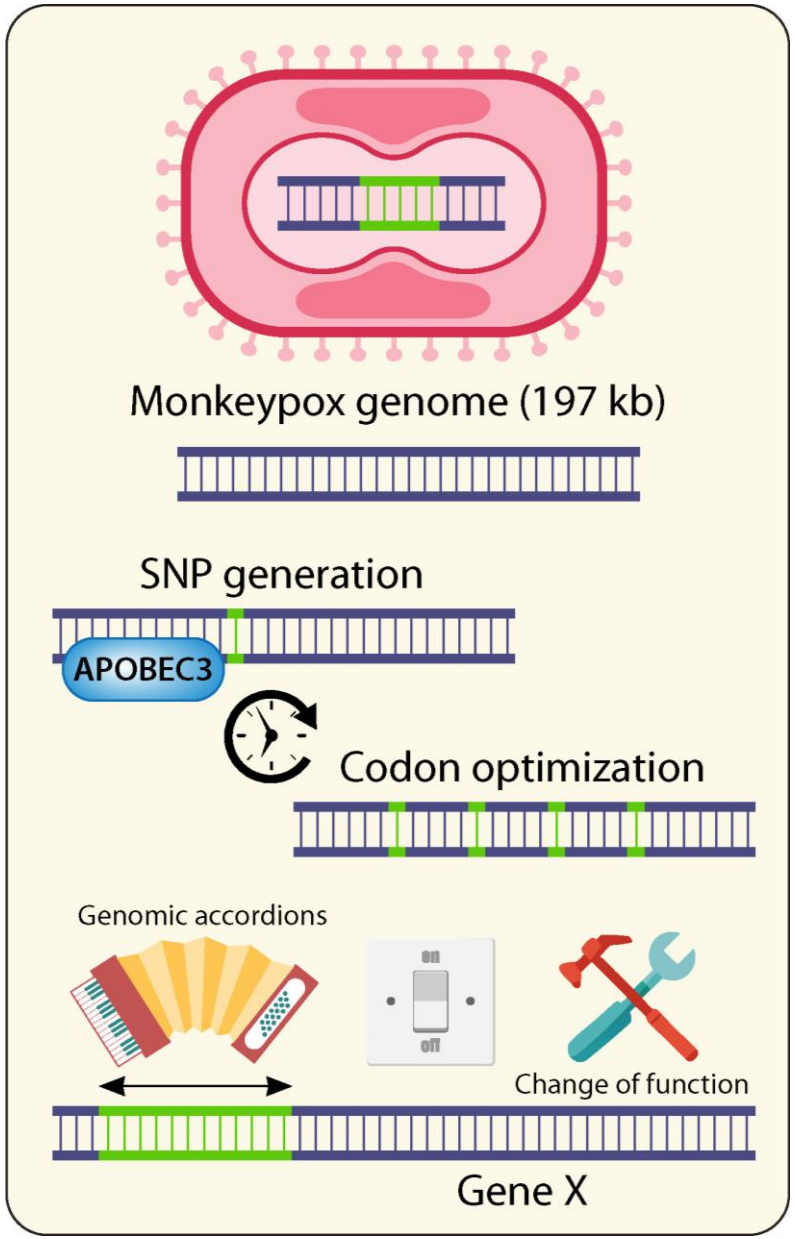
Fig. 1 | Spatiotemporal and host species distributions of MPXV sequences (worldwide, 1958–2024). a, Maximum likelihood phylogenetic tree highlighting the major clades of MPXV. The branches are colored by clade. Lineage B.1 clusters within clade IIb and caused the 2022 global MPXV outbreak; this lineage is therefore separated from the remainder of clade IIb. The scale bar shows the expected number of nucleotide substitutions per site. A subset of clades are collapsed for clarity. **b**, The temporal and regional distribution of MPXV sequences is shown for each clade. The *n* numbers show the total number of sequences from the clade. **c**, Distributions of the number of sequences from each host species.

- Dal **1977**, la cessazione della vaccinazione antivaiolosa ha comportato una **diminuzione dell'immunità** e un **aumento della popolazione suscettibile all'Mpox**, ovvero si è creato un **ambiente favorevole al RITORNO DELL'MPXV**, dimostrato da:

    - *Aumento dei casi confermati*
    - *Focolai in alcune regioni dopo un intervallo di 30-40 anni*
    - *Aumento dell'età delle persone affette da Mpox*

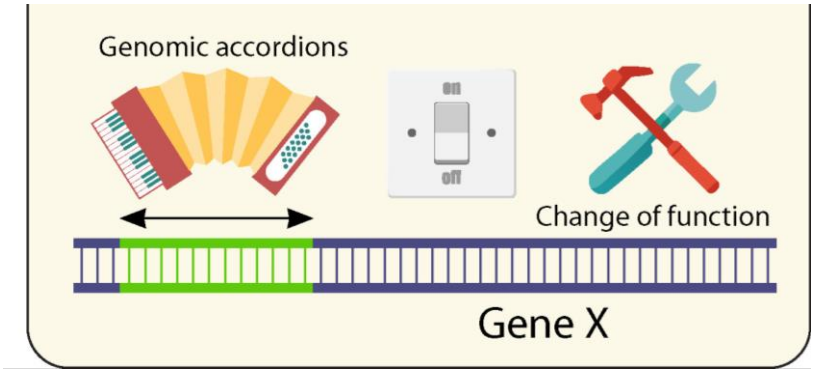
- A partire dagli anni '80 la trasmissibilità del virus del vaiolo delle scimmie è aumentata di circa *venti volte.*





Two evolutionary mechanisms acting upon MPXV, which “fine-tunes” their gene products to better adapt to human hosts: APOBEC3 mutations and employment of genomic accordions

There were observed APOBEC3 mutations in MPXV’s Clade IIb B.1 genes: OPG023: ANK/F-box protein and host-range factor; OPG047: BTB-kelch domain contributor of virulence and lesion size; OPG071: DNA polymerase catalytic subunit; OPG105: RNA polymerase subunit; OPG109: RNA polymerase-associated protein; OPG153: an intracellular mature virion surface tubule protein; OPG188: a poxin-schlafen like protein; and OPG210: a surface glycoprotein and T-cell response suppressor (28). While the mutations have not been experimentally determined to be the drivers of increased human-to-human transmission, there are reported codon biases that are preferentially used in human hosts (69). The SNP mutations within ankyrin-containing and BTB-kelch proteins may alter species-specific binding requirements for the stimulation of their target host proteins.
Interestingly, OPG188 was also revealed to be more prone to mutation within MPXV compared to other accessory genes across the genome (28). OPG188 codes for a schlafen-like protein, which are RNA-binding proteins expressed in response to IFN, and plays a role in growth inhibition during an anti-viral state (70). OPG188 also has a conjoined poxin domain that interferes with the STING-dependent interferon pathway via functioning as a cGAMP-specific nuclease (1).



In response to selective pressure, the high duplication rate of the Orthopoxvirus genome allows for increases in gene copy number to overcome a host's pressure

Short tandem repeats (STRs) are located across the MPXV genome—positioned in intergenic regions or even within coding regions (34, 75). The expansion and retraction in the length of the STRs, much like genomic accordions, can induce frameshift mutations that can turn off, or conversely, turn on genes

There were three major identified accordions that have a functional impact.

The first of which is a STR placed at the start of the reading frame for OPG208, coding for SPI-1, a serine protease that blocks multiple steps of IL-1 processing and cell death cascades (34). This STR produced an alternative start codon, which is transcribed *in vitro*, and incorporated 52 copies of human-associated TAC codons (34). The increased length of the STR more closely resembles the SPI-1 gene in Clade I MPXV (29).

The second is another alternative methionine start codon, built by an STR accordion, upstream of OPG 204, a secreted decoy receptor for type I IFN (34). This alternative start codon is also transcribed *in vitro,* although the functional implications of an extended N-terminal Met-Lys repeat remain unknown.

Finally, there is predicted inactivation of OPG153, a protein that attaches virions to laminin and regulates their egress, which is also a major epitope targeted by the host antibody response (34). This gene contains a poly-D accordion and the insertion of two isoleucines, resulting in a structurally similar OPG153 in Clade IIb, which closely resembles Clade I's ortholog of OPG153 rather than sister Clade IIa's ortholog (34). Throughout the history of Orthopoxviruses, this protein has been lost on 18 independent occasions, and its loss has been both shown to attenuate the virus as well as compensate for the loss of a missing transcription factor gene

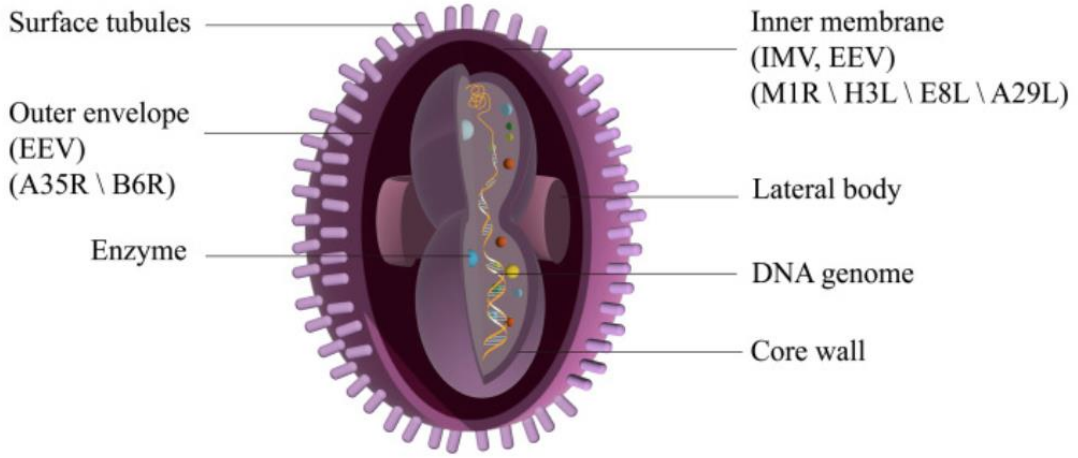
https://doi.org/10.1128/msphere.00576-24

Secondo l'OMS l'epidemia di MPXV raramente si potrebbe trasformare in una pandemia, dal momento che l'**infettività del virus è piuttosto bassa**.

Questa recente e rapida ondata di nuovi casi in aree non endemiche ha suggerito che MPXV abbia subito un ***processo evolutivo***, una potenziale evoluzione genetica, che ha visto la formulazione di alcune ipotesi a favore:

La repentina evoluzione e la **capacità di MPXV di adattarsi all'essere umano** incrementa la sopravvivenza del virus, nonché la suscettibilità dell'uomo a quest'ultimo.

mutazione H3L e passaggio di MPXV tra specie diverse → adattamento all'uomo e miglioramento della trasmissione



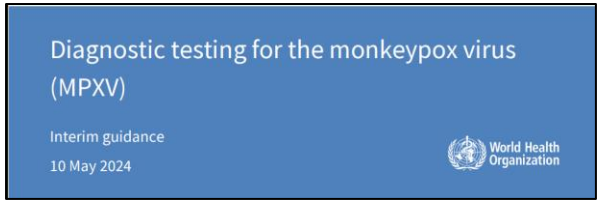
MPXV

https://doi.org/10.1016/j.ijbiomac.2023.125515

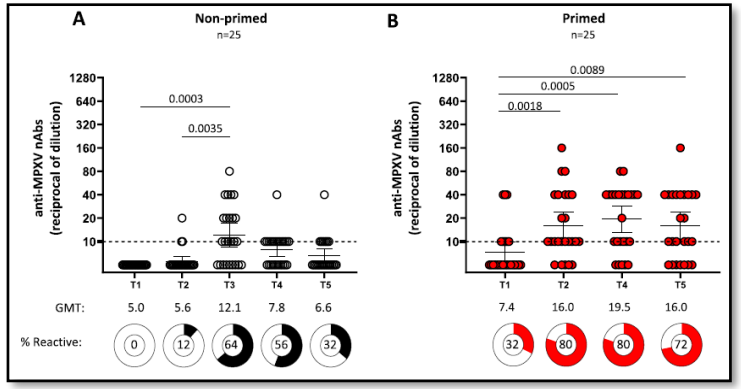
Epidemic response and management

Actions

Laboratory diagnosis



Immune response to infection and vaccination



Viral kinetics in the human host

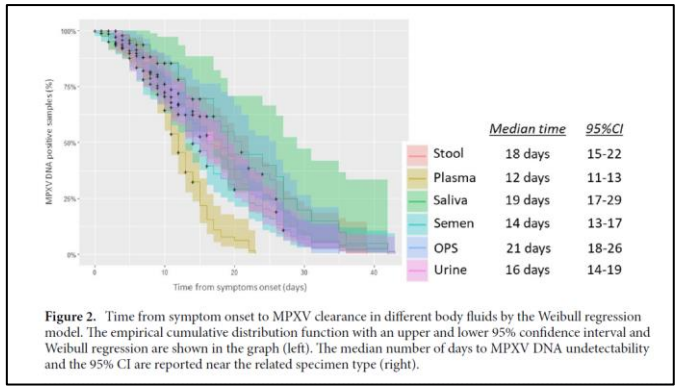
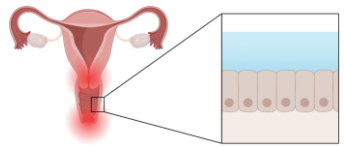


Figure 2. Time from symptom onset to MPXV clearance in different body fluids by the Weibull regression model. The empirical cumulative distribution function with an upper and lower 95% confidence interval and Weibull regression are shown in the graph (left). The median number of days to MPXV DNA undetectability and the 95% CI are reported near the related specimen type (right).

Genital tropism



Vaccination against mpox as a countermeasure to the global and local spread

Vaccination with a third-generation smallpox vaccine the Modified Vaccinia Ankara–Bavaria Nordic [MVA–BN] become a crucial component of the outbreak control (Imvanex)

This third-generation smallpox vaccine has the advantage that it cannot reproduce complete virions in human cells, "the block of the MVA life cycle occurs at the step of virion assembly resulting in assembly of immature virus particles that are not released from the infected cell

Higher burden of Mpox in people living with HIV (PLWH) with low CD4+T cell counts

Mpox vaccination campaign in Italy:2025

- Laboratory personnel and HCWs
- People travelling to countries with Mpox outbreaks
- People who met sexual habit–associated risk criteria…

Delivering a two-dose schedule in naïve and a single dose to smallpox vaccine-experienced.
In immunocompromised individuals 2 doses even if experienced

SC or ID inoculation (>12 years old)

A booster dose is possible two years after the primary cycle

Post exposure prophilaxis possible ideally 4 to14 days from the contact with a case

(Circolare ministeriale vedasi allegato tecnico per ulteriori dettagli)

MPXV and the Male Genital tract

Monkeypox virus isolation from a semen sample collected in the early phase of infection in a patient with prolonged seminal viral shedding

MPXV DNA kinetics in bloodstream and other body fluids samples

Silvia Meschi[1,7], Francesca Colavita[1,7], Fabrizio Carletti[1], Valentina Mazzotta[2], Giulia Matusali[1✉], Eliana Specchiarello[1], Tommaso Ascoli Bartoli[2], Annalisa Mondi[2], Claudia Minosse[1], Maria Letizia Giancola[2], Carmela Pinnetti[2], Maria Beatrice Valli[1], Daniele Lapa[1], Klizia Mizzoni[1], David J. Sullivan[4], Jiangda Ou[5], Daniele Focosi[6], Enrico Girardi[3], Emanuele Nicastri[2], Andrea Antinori[2] & Fabrizio Maggi[1]

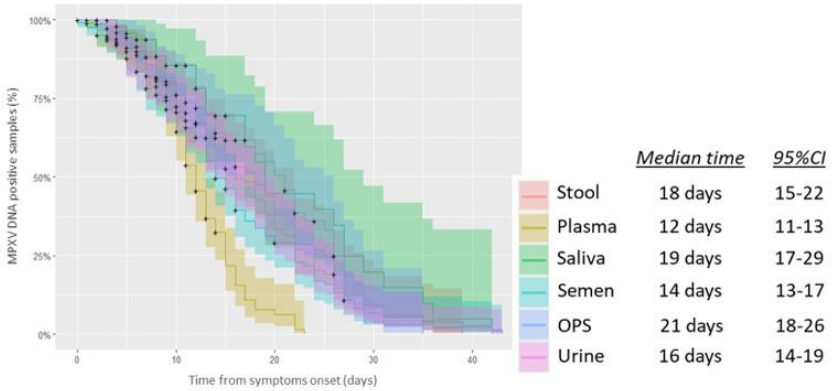


Figure 2. Time from symptom onset to MPXV clearance in different body fluids by the Weibull regression model. The empirical cumulative distribution function with an upper and lower 95% confidence interval and Weibull regression are shown in the graph (left). The median number of days to MPXV DNA undetectability and the 95% CI are reported near the related specimen type (right).

MPXV and the Male Genital tract

nature microbiology

Article

https://doi.org/10.1038/s41564-022-01259-w

Retrospective detection of monkeypox virus in the testes of nonhuman primate survivors

Received: 23 June 2022

Accepted: 26 September 2022

Published online: 17 October 2022

Jun Liu[1], Eric M. Mucker[1], Jennifer L. Chapman[1,2], April M. Babka[1], Jamal M. Gordon[1], Ashley V. Bryan[1], Jo Lynne W. Raymond[1], Todd M. Bell[1], Paul R. Facemire[1], Arthur J. Goff[1], Aysegul Nalca[1] and Xiankun Zeng[1]

Table 1 | Two macaque survivors with testicular monkeypox virus persistence

Survivors	Date of challenge	Days PE	Exposure dose, strain and route	MPXV IHC in testis	MPXV IHC in epididymis	MPXV IHC in prostate	Other IHC-positive tissues/organs
6	25/2/2008	37	5×10^6 p.f.u., Clade I strain, IT	Pos	Neg	Neg	Tracheobronchial L.N. and skeletal muscle
15	7/11/2006	21	5×10^5 p.f.u., Clade I strain, IT	Pos	Neg	Neg	Lung

PE, post-exposure; p.f.u., plaque-forming unit; L.N., lymph node; Neg, IHC-negative; Pos, IHC-positive; Clade I strain refers to Zaire 1979 str

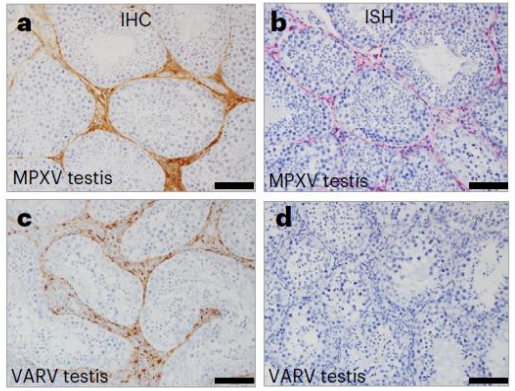


Fig. 2 | A monkeypox virus-specific RNA in situ hybridization method. a–d, MPXV antigen (brown in **a**) and RNA (red in **b**) were detected in MPXV-infected testicular tissue using IHC and RNA ISH, respectively. VARV antigen (brown in **c**) was detected in VARV-infected testicular tissue using IHC, but VARV RNA was undetectable (**d**) using MPXV-specific RNA ISH probe. Representative IHC and ISH staining images shown from $n = 3$ (**a–d**) biologically independent animals. Nuclei were counterstained blue with hematoxylin. Scale bar, 50 µm.

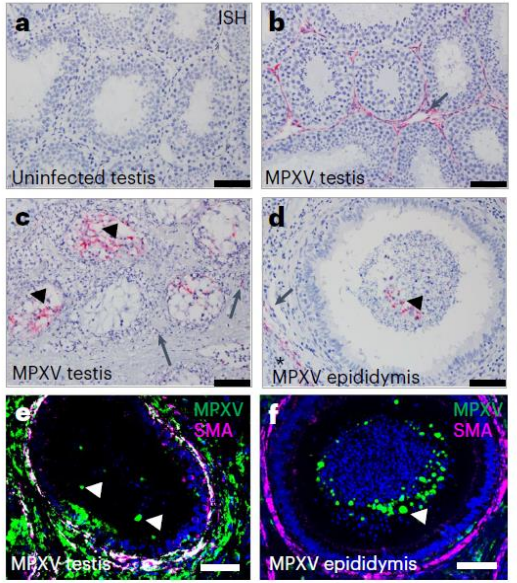
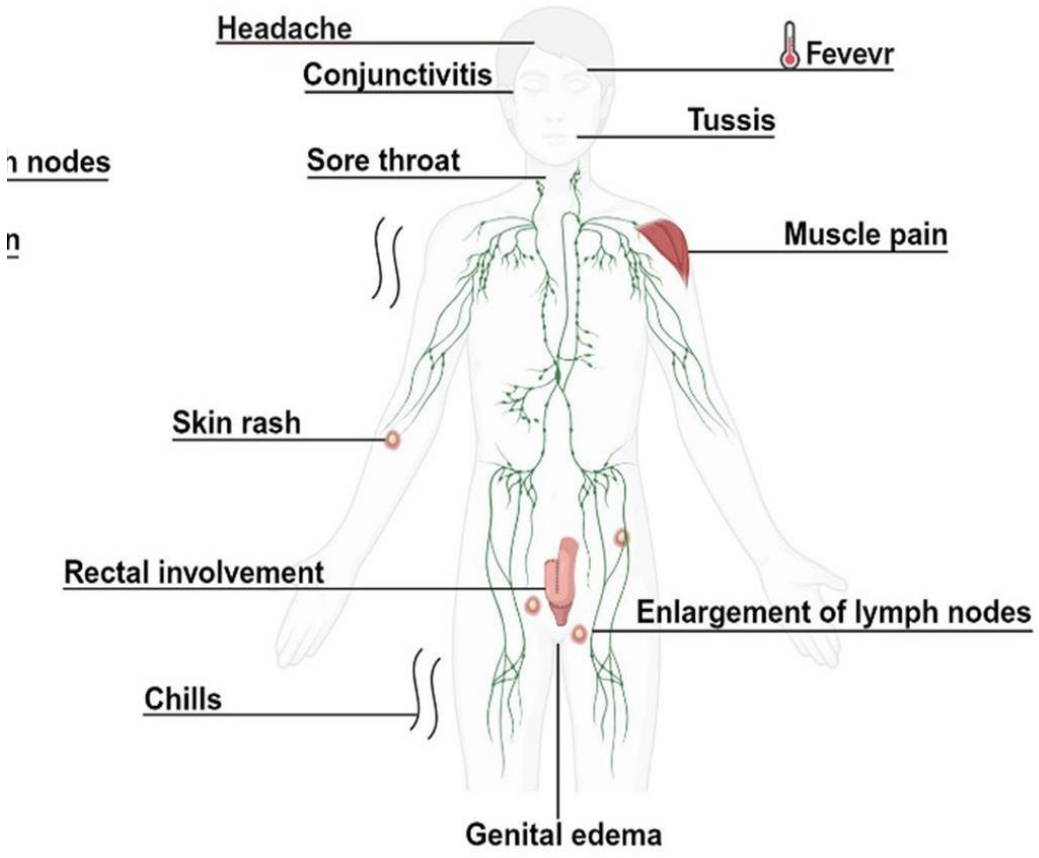


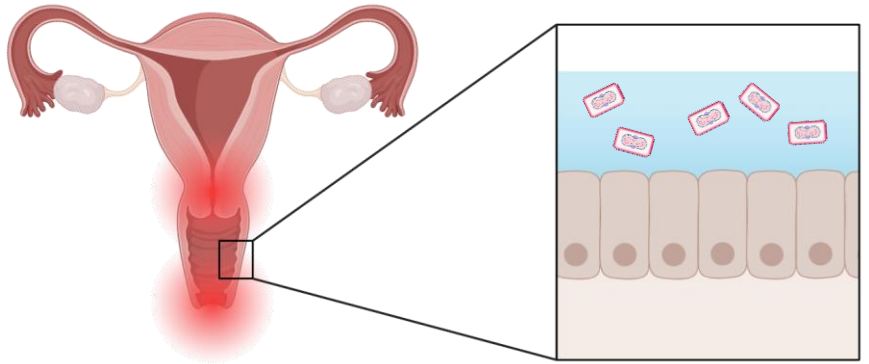
Fig. 3 | Monkeypox virus in the seminiferous tubules of testes and epididymal lumina. a–d. Testicular (**a–c**) and epididymal (**d**) tissue sections stained

- The GT may represent a portal of entry for the MPXV
- MPXV in semen may determine sexual transmission
- The infection of the FGT may determine the vertical transmission of MPXV



In the 2022 Mpox outbreak, rashes primarily appeared around the genital area, with lymphadenopathy first occurring in the groin.

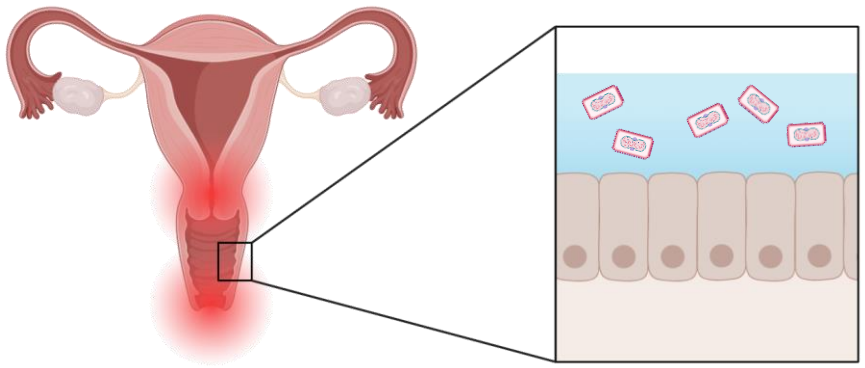
Site of positive monkeypox viral PCR — no. (%)†	
Skin or anogenital lesion	512 (97)
Nose or throat swab	138 (26)
Blood	35 (7)
Urine	14 (3)
Semen	29 (5)



Vulvar rash and vaginal inflammation

MPXV presence in vaginal fluids

MPXV and the Female Genital tract



Vulvar rash and vaginal inflammation

MPXV presence in vaginal fluids

Mpox in Pregnancy — Risks, Vertical Transmission, Prevention, and Treatment

n engl j med 391;14 nejm.org October 10, 2024

Jean B. Nachega, M.D., Ph.D., M.P.H., Emma L. Mohr, M.D., Ph.D., Pradip Dashraath, M.B., B.S., M.Med., Placide Mbala-Kingebeni, M.D., Ph.D., Jean R. Anderson, M.D., Landon Myer, M.D., Ph.D., Monica Gandhi, M.D., David Baud, M.D., Ph.D., Lynne M. Mofenson, M.D., and Jean-Jacques Muyembe-Tamfum, M.D., Ph.D., for the Mpox Research Consortium (MpoxReC)

The limited available data suggest that mpox increases the risks of severe maternal disease, miscarriage, and stillbirth. A 2024 systematic review of seven studies identified 32 pregnant women with clade IIb MPXV infection between 6 and 31 weeks of gestation. Of the 12 pregnancies with reported gestational outcomes, half resulted in intrauterine fetal demise.

Article | Published: 22 April 2024

Infection with mpox virus via the genital mucosae increases shedding and transmission in the multimammate rat (*Mastomys natalensis*)

Julia R. Port, Jade C. Riopelle, Samuel G. Smith, Lara Myers, Franziska K. Kaiser, Matthew C. Lewis, Shane Gallogly, Atsushi Okumura, Trent Bushmaker, Jonathan E. Schulz, Rebecca Rosenke, Jessica Prado-Smith, Aaron Carmody, Sidy Bane, Brian J. Smith, Greg Saturday, Heinz Feldmann, Kyle Rosenke ✉ & Vincent J. Munster ✉

Nature Microbiology **9**, 1231–1243 (2024) | Cite this article

Mucosal inoculation via the rectal, vaginal and aerosol routes led to increased shedding, replication and a pro-inflammatory T cell profile compared with skin inoculation. Transmission might be sustained by increased susceptibility of the anal and genital mucosae for infection and subsequent virus release.

MPXV vertical transmision

pregnant women are considered a high-risk category because of MPXV infection may determine pregnancy complications, severe congenital infections, and perinatal morbidity and mortality.

Maternal-fetal transmission of Clade Ia MPXV has been demonstrated through the detection of the virus in fetal tissue biopsies and autopsies, amniotic fluid, and cord blood (Rossi B. et al. 2025).

Additionally, in a meta-analysis and systematic review conducted by Clemente Sanchez end colleagues, in 2024, MPXV-specific IgM has been identified in serum or cerebrospinal fluid (CSF) in children within a few days of birth (Clemente S. et al. 2024).

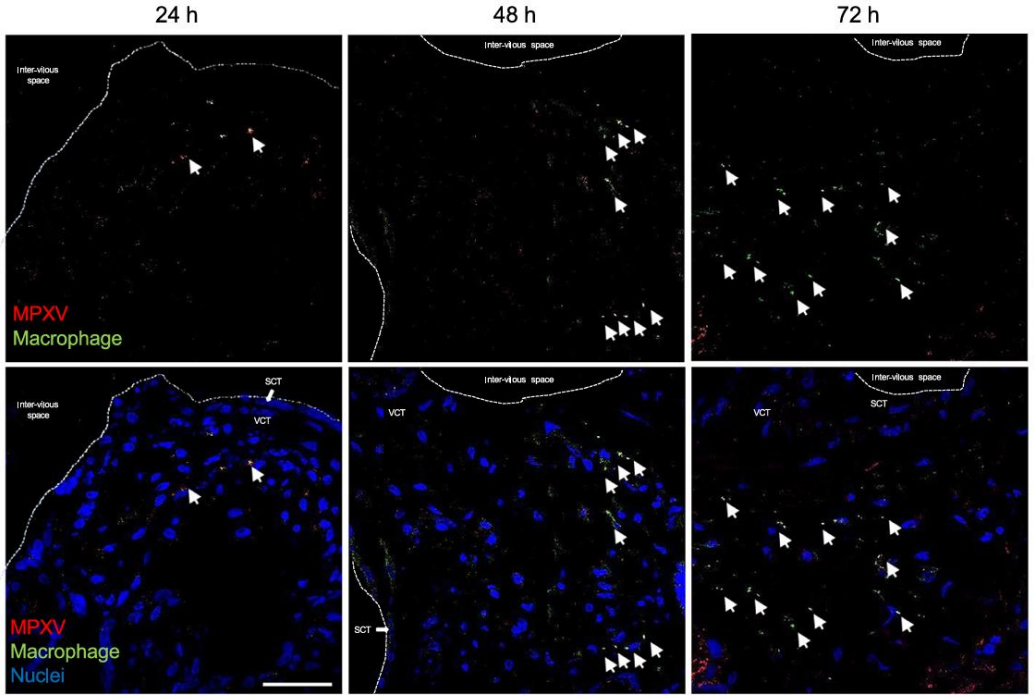
clade IIb MPXV infection was reported in 32 pregnant women between 6 and 31 weeks of gestation . Of the 12 pregnancies with reported gestational outcomes, half resulted in intrauterine fetal demise (Clemente N.S. et al. 2024). MPXV can be transmitted from mother to fetus, with high viral loads, found within fetal and maternal-fetal interface tissues, possibly contributing to pregnancy loss (Nachega J.B. et al. 2024).

MPXV vertical transmision

The potential for intrauterine transmission is further supported by data from nonhuman primates: a macaque model showed vertical transmission 6 to 14 days after infection, followed shortly by fetal demise (Nachega J.B. et al. 2024).

Monkeypox Virus Subverts the Inflammatory Response of Macrophages at the Maternal-Fetal Interface

Jonatane Andrieu[1] | Margaux Valade[2] | Nathalie Wurtz[2] | Marion Lebideau[2] | Florence Bretelle[2,3] | Bernard La Scola[2] | Jean-Louis Mège[1,4] | Soraya Mezouar[1,5]



Antivirals

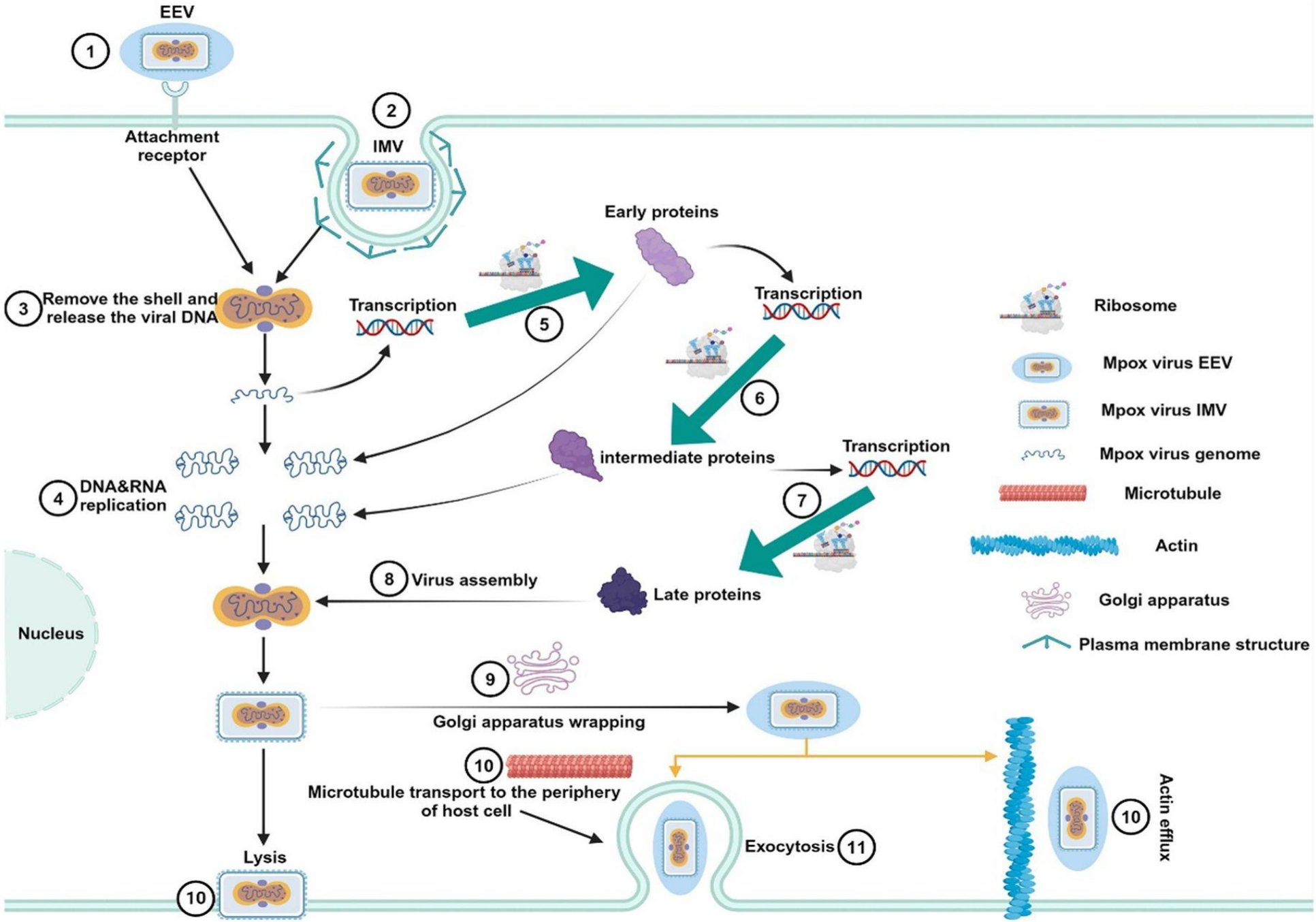
Although there are no specific antivirals for Mpox, some antivirals (Tecovirimat, Brincidofovir, Cidofovir) have been explored.
Tecovirimat (ST-246 or TPOXX®), was approved (for smallpox) by FDA in 2018 and approved by European Medicines Agency in January 2022 for treatment of smallpox and cowpox.
Tecovirimat inhibits VP37 (p37) protein of VACV by targeting the viral F13L gene. VP37, a highly conserved protein in OPXV genus, is required for viral maturation and release from the infected cell. Inhibition of VP37 prevents viral spread within an infected animal model.

Preclinical investigations have confirmed the efficacy of Tecovirimat in treating Mpox (Alakunle et al. 2024).

Antivirals

Cidofovir (CDV or Vistide®) prodrug is an acyclic nucleoside phosphate that was approved by FDA in 1996 for the treatment of retinitis (caused by cytomegalovirus) in AIDS patients.
The efficacy of CDV has been identified during the in vitro studies in MPXV-infected animals, but the clinical data of CDV efficacy against mpox in human are not available (Alakunle et al. 2024).

Brincidofovir (CMX001), a CDV derivative, was approved for smallpox treatment in 2021 by FDA, and is in first line for treatment after Tecovirimat, and it has lesser toxic effects than Cidofovir (Alakunle et al. 2024). Brincidofovir showed promise against a variety of DNA viruses, most notably adenoviruses and cytomegalovirus (CMV), with a particular emphasis on poxviruses like Mpox.
However, the evaluation of CMX001 efficacy and safety in human mpox through the clinical trials is needed (Alakunle et al. 2024).


EEV
1
Attachment receptor
2
IMV
3 Remove the shell and release the viral DNA
Transcription
5
Early proteins
Transcription
6
intermediate proteins
Transcription
7
4 DNA&RNA replication
8 Virus assembly
Late proteins
Nucleus
9
Golgi apparatus wrapping
10
Microtubule transport to the periphery of host cell
Exocytosis 11
Lysis
10
10
Actin efflux
Ribosome
Mpox virus EEV
Mpox virus IMV
Mpox virus genome
Microtubule
Actin
Golgi apparatus
Plasma membrane structure

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Original Article

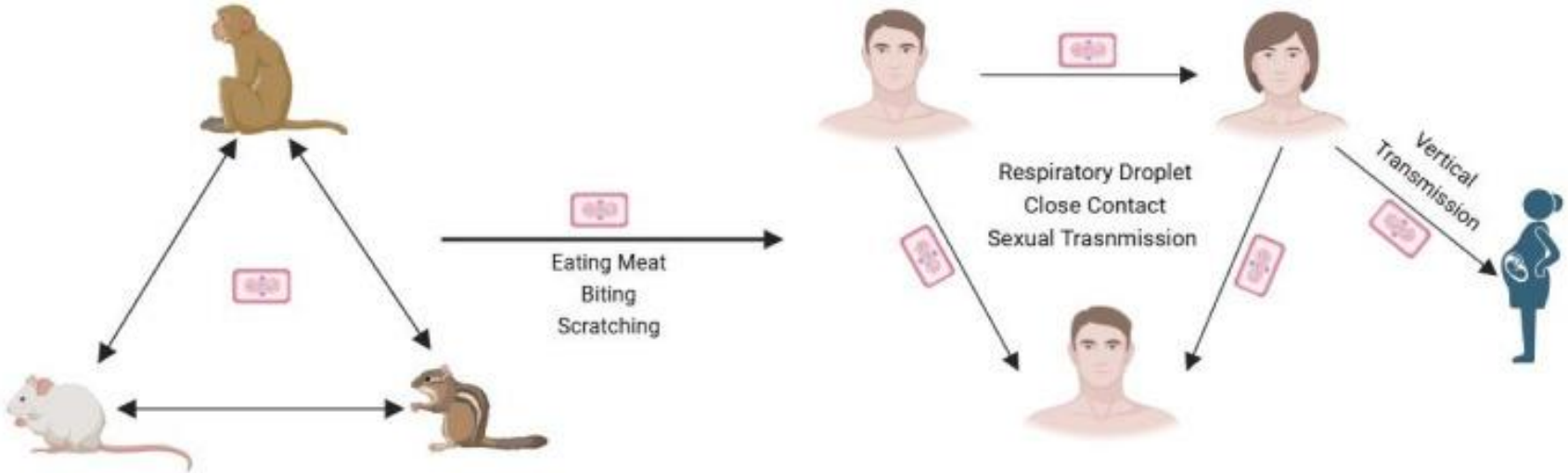
Complete Genome Sequencing, Annotation, and Mutational Profiling of the Novel Clade I Human Mpox Virus, Kamituga Strain

Leandre Murhula Masirika[1,2#], Anuj Kumar[3,4,5#], Mansi Dutt[3,4,5#], Ali Toloue Ostadgavahi[3,4], Benjamin Hewins[3,4], Maliyamungu Bubala Nadine[6], Bilembo Kitwanda Steeven[6], Franklin Kumbana Mweshi[6], Léandre Mutimbwa Mambo[7], Justin Bengehya Mbiribindi[8], Freddy Belesi Siangoli[8], Alyson A Kelvin[9], Jean Claude Udahemuka[10], Patricia Kelvin[3,5], Luis Flores[1,11,12,13], David J Kelvin[3,4,5], Gustavo Sganzerla Martinez[3,4,5]

We observed that seven proteins, namely OPG047, OPG080, OPG105, OPG143, OPG151, OPG153, and OPG210 have emerged as hot spot mutations… a deletion of OPG032 gene in all six samples

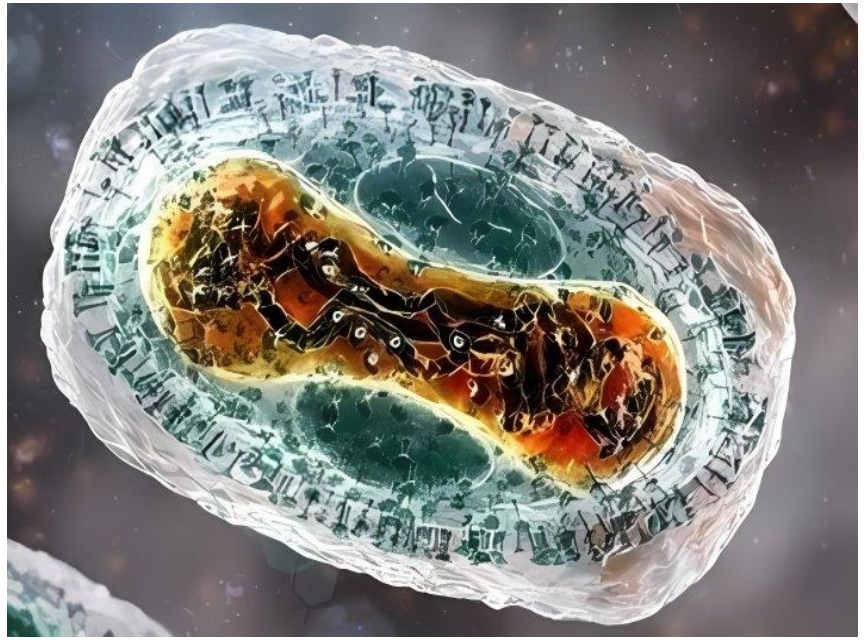
Partial deletion of the OPG164 (A36R) transmembrane phosphoprotein in monkeypox virus clade Ib/sh2023 disrupts the active region involving Tyr140

Deletion of the phosphorylated Tyr140 and neighbouring residues in clade Ib mpox might disrupt the activation of the host Arp2/3 complex, leading to no actin tail formation and decreased cell-to-cell pathogenicity, explaining in part the possible reduced human pathology of monkeypox virus clade Ib or sustained human-to-human transmission


Eating Meat
Biting
Scratching
Respiratory Droplet
Close Contact
Sexual Trasnmission
Vertical
Transmission

Le differenze più significative tra i due cladi si riscontrano nei geni di virulenza:

- **BR-203** → Codifica per una proteina che previene l'apoptosi dei linfociti infetti. Assente nel virus Variola.
- **BR-209** → Codifica per una proteina legante IL-1β. Assente nel virus Variola.
- **COP-C3L** → Codifica per MOPICE ("monkeypox inhibitor of complement enzymes"). Presente nel clade dell'Africa centrale ma non in quello dell'Africa occidentale.



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