A tale of two clades: monkeypox viruses

PERSPECTIVE

Urgent need for a non-discriminatory and non-stigmatizing nomenclature for monkeypox virus

New nomenclature for mpox (monkeypox) and monkeypox virus clades

In May, 2015, WHO recommended best practices for naming new infectious diseases to avoid offense or economic effect for any ethnic, regional, or other groups. Although mpox (formerly known as monkeypox) is not new, WHO has endorsed mpox as the new name for this re-emerging disease and backed the
## What’s In a Name?

<table>
<thead>
<tr>
<th>Name</th>
<th>Poxvirus Example</th>
<th>Coronavirus Example</th>
<th>Who Creates?</th>
<th>Who Updates?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disease</td>
<td>• Monkeypox virus</td>
<td>• 2019-nCoV</td>
<td>WHO</td>
<td>WHO</td>
</tr>
<tr>
<td></td>
<td>• <strong>MPOX</strong></td>
<td>• hCoV-19</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• <strong>COVID-19</strong></td>
<td>• <strong>COVID-19</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Virus</td>
<td><strong>Monkeypox virus</strong></td>
<td><strong>SARS-CoV-2</strong></td>
<td>Discoverer</td>
<td>Scientific community</td>
</tr>
<tr>
<td>Clade</td>
<td>• West African; DRC, Congo Basin</td>
<td>• <strong>Alpha, Beta, Gamma, Delta, Omicron...</strong></td>
<td>Scientific community (WHO-consulted)</td>
<td>Scientific community (WHO-consulted)</td>
</tr>
<tr>
<td>Species</td>
<td>• <strong>Monkeypox virus</strong></td>
<td>• <strong>Severe acute respiratory syndrome-related coronavirus</strong></td>
<td>ICTV</td>
<td>ICTV</td>
</tr>
<tr>
<td></td>
<td>• <strong>Orthopoxvirus monkeypox</strong></td>
<td>• <strong>Betacoronavirus pandemic</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
# Human Orthopoxvirus Disease

## Smallpox
- First identified: 1100 – 1500 BCE
- Host range: Exclusively human
- Symptoms: Rash, fever, aches, vomiting, hemorrhage
- Case fatality rate: 1-30%
  - Dependent on particular clade and vaccination status
- Human-human transmission rate:
  - ~60% (30 - 90%)
- Extinct
- Eradication (vaccination) campaign

## MPOX
- First identified: 1958 monkey colonies; 1970 human case
- Host range: Rodents, zoonotic transmission to primates and humans
- Symptoms: Rash, fever, aches, vomiting, lymphadenopathy
- Case fatality rate: 0 - 10%
  - Dependent on particular clade and vaccination status
- Human-human transmission rate:
  - ~10% (3 - 15%)
- Rodent reservoir
- Increasing incidence
  - Human encroachment on animal reservoir habitats
  - Waning vaccination status of population
  - Increased human-human transmission
MPOX Cases in Africa 1970 - 1986

West Africa: 6 cases

Congo Basin: 260 cases

Origination of rodent shipment to the US

CDC – 2005; Sammons et. al.
U.S. Midwest MPOX Outbreak 2003

- April – June, 2003
- Infected rodents imported into the U.S. from West Africa
- Rodents housed with native prairie dogs
  - Infected prairie dogs transmitted virus to humans
  - Transmission due to respiratory and direct mucocutaneous exposure
- 72 confirmed or suspected human cases
  - No human fatalities
  - No human-human transmission
World-wide MPOX Outbreak 2022 - Present

◆ Total
  ◆ Cases: 95,000
  ◆ Deaths: 181 (0.2%)
  ◆ Countries: 117

◆ February 2024
  ◆ Cases: 715
  ◆ Deaths: 2 (0.28%)
  ◆ Countries: 29

World Health Organization, 20 March 2024
https://worldhealthorg.shinyapps.io/mpx_global/
Monkeypox virus the species vs. Monkeypox virus the sub-species
Demarcation Criteria *Poxviridae: Subfamily: Genera: Species*

- **Phenotypic**
  - Natural host range (Subfamily)
  - Growth characteristics and host range in cell culture
    - Morphology of pocks; Plaque characteristics
  - Disease characteristics.
    - Morbidity, mortality, etc.
- **Serological criteria**
  - Plaque neutralization tests, cross-protection in animals

- **Genotypic**
  - Gene content
  - Genome organization
  - Amino acid sequence identity of commonly shared genes.
    - Hemagglutinin or A-type inclusion protein
  - Nucleotide sequence identity, conserved, core region of orthopoxvirus genomes
    - Different species <96% - 98%
    - Isolate >98%
- **Phylogenetic analysis**
Poxviridae Family

Orthopoxvirus
- genus
- subfamily

Centapoxvirus
- Suiapoxvirus
- Capripoxvirus
- Cervidapoxvirus
- Leporipoxvirus
- Oryzopoxvirus
- Yatapoxvirus
- Vesperitillionpoxvirus
- Pleropoxvirus
- Mustelpoxvirus

Parapoxvirus
- Sciuripoxvirus
- Molluscipoxvirus
- Macropoxvirus

Avipoxvirus
- Crocdyloidapoxvirus
- Salmonpoxvirus

Betaentomopoxvirus
- Entomopoxvirinae

Alphaentomopoxvirus
- Delataentomopoxvirus

<table>
<thead>
<tr>
<th>Genus</th>
<th>Subfamily</th>
</tr>
</thead>
<tbody>
<tr>
<td>Orthopoxvirus</td>
<td></td>
</tr>
<tr>
<td>Centapoxvirus</td>
<td></td>
</tr>
<tr>
<td>Suiapoxvirus</td>
<td></td>
</tr>
<tr>
<td>Capripoxvirus</td>
<td></td>
</tr>
<tr>
<td>Cervidapoxvirus</td>
<td></td>
</tr>
<tr>
<td>Leporipoxvirus</td>
<td></td>
</tr>
<tr>
<td>Oryzopoxvirus</td>
<td></td>
</tr>
<tr>
<td>Yatapoxvirus</td>
<td></td>
</tr>
<tr>
<td>Vesperitillionpoxvirus</td>
<td></td>
</tr>
<tr>
<td>Pleropoxvirus</td>
<td></td>
</tr>
<tr>
<td>Mustelpoxvirus</td>
<td></td>
</tr>
<tr>
<td>Parapoxvirus</td>
<td></td>
</tr>
<tr>
<td>Sciuripoxvirus</td>
<td></td>
</tr>
<tr>
<td>Molluscipoxvirus</td>
<td></td>
</tr>
<tr>
<td>Macropoxvirus</td>
<td></td>
</tr>
<tr>
<td>Avipoxvirus</td>
<td></td>
</tr>
<tr>
<td>Crocdyloidapoxvirus</td>
<td></td>
</tr>
<tr>
<td>Salmonpoxvirus</td>
<td></td>
</tr>
<tr>
<td>Betaentomopoxvirus</td>
<td></td>
</tr>
<tr>
<td>Entomopoxvirinae</td>
<td></td>
</tr>
<tr>
<td>Alphaentomopoxvirus</td>
<td></td>
</tr>
<tr>
<td>Delataentomopoxvirus</td>
<td></td>
</tr>
</tbody>
</table>
Orthopoxvirus Genus

- AY243312 vaccinia virus
- DQ792504 horsepox virus
- DQ437594 taterapox virus
- AF438165 camelpox virus
- X69198 variola major virus / variola virus
- Y16780 variola minor virus
- AF380138 monkeypox virus (clade I)
- AY753185 monkeypox virus (clade IIa)
- AF482758 cowpox virus
- MH816996 orthopoxvirus Abatino
- AF012825 ectromelia virus
- MH607141 Akhmeta virus
- KU749312 skunkpox virus
- KU749311 volepox virus
- KP143769 raccoonpox virus

species

- Vaccinia virus
- Taterapox virus
- Camelpox virus
- Variola virus
- Monkeypox virus
- Cowpox virus
- Abatino macacapox virus
- Ectromelia virus
- Akhmeta virus
- Skunkpox virus
- Volepox virus
- Raccoonpox virus
Genomic epidemiology of mpox viruses across clades

Host:
- Homo sapiens
- Pan troglodytes verus
- Cricetomys gambianus
- Cynomys
- Funisciurus

Clades:
- Clade I
- Clade II
  - Clade IIa
  - Clade IIb

Divergence:
- 2022, 2024
- 2018 - 2019
- 2019 - 2023
- 2017, 2018
- 1971
- 1970
- 1978, 1985, 2006
- 2003 - 2023
Variability of MPOX Infections
Clade I vs. II

- **Clade I**
  - Congo basin
    - Pre 2022, >90% of reported cases
    - Case fatality rate: 1-5% to >10%
  - Zoonotic outbreaks
    - Human-human transmission (limited)

- **Clade II**
  - West African
    - CFR (pre-2022): 0-4%
    - Zoonotic outbreaks
      - Human-human transmission: none (very limited)
    - Source of 2003 US Midwest outbreak virus (Clade IIa)
  - World-wide outbreak 2022 (Clade II.b B.1)
    - CFR: 0.2%
    - Human-human transmission
      - STD, Male (96%); MSM (84%)
Orthopoxviruses: Mechanisms of Variation
Orthopoxvirus Gene Content

Gene Status:
- Intact
- Truncated
- Fragmented
- Missing

Gene Count

- CPXV-GRI
- CPXV-Ger
- CPXV-BR
- HSPV
- ECTV
- RPXV
- VACV-WR
- TATV
- CMLV
- VACV-Cop
- MPXV-ZAI
- MPXV-WR
- VARV-BRZ
- VARV-SLN
- VARV-KUW
- VARV-SAF
- VACV-MVA
Variola: 8 unique genes
Monkeypox: 20 unique genes
Cowpox: 0 unique genes
Clade I: 3 unique genes
Clade II: 0 unique genes
Specific enrichment of APOBEC3-type mutations in MPXV samples collected since 2017.
Evolution of Monkeypox virus

- Host dependent
  - Long periods of variation in an unknown reservoir host
  - Periodic zoonoses into alternative hosts
    - Primate species; Humans
  - More extended transmission in human hosts
    - Clade IIb

- Mechanisms of genotypic variation
  - SNPs, small indels
  - APOBEC3-driven mutagenesis

- Extent of phenotypic variation
  - Clade I and II: CFR, transmission differences (?)
  - Within Clade II: Limited to none (?)
Thanks To

- UAB Alumni
  - Eneida Hatcher
  - Mary Odom
  - Brett Pickett
  - Chunlin Wang

- Current UAB
  - Don Dempsey
  - Curtis Hendrickson
  - Login Mims
  - Steve Powell

- ICTV
  - Executive Committee
  - SG Members

- Collaborators
  - Mark Buller
  - Chris Upton
  - CDC Team