Clinical Presentations and Management of Mpox

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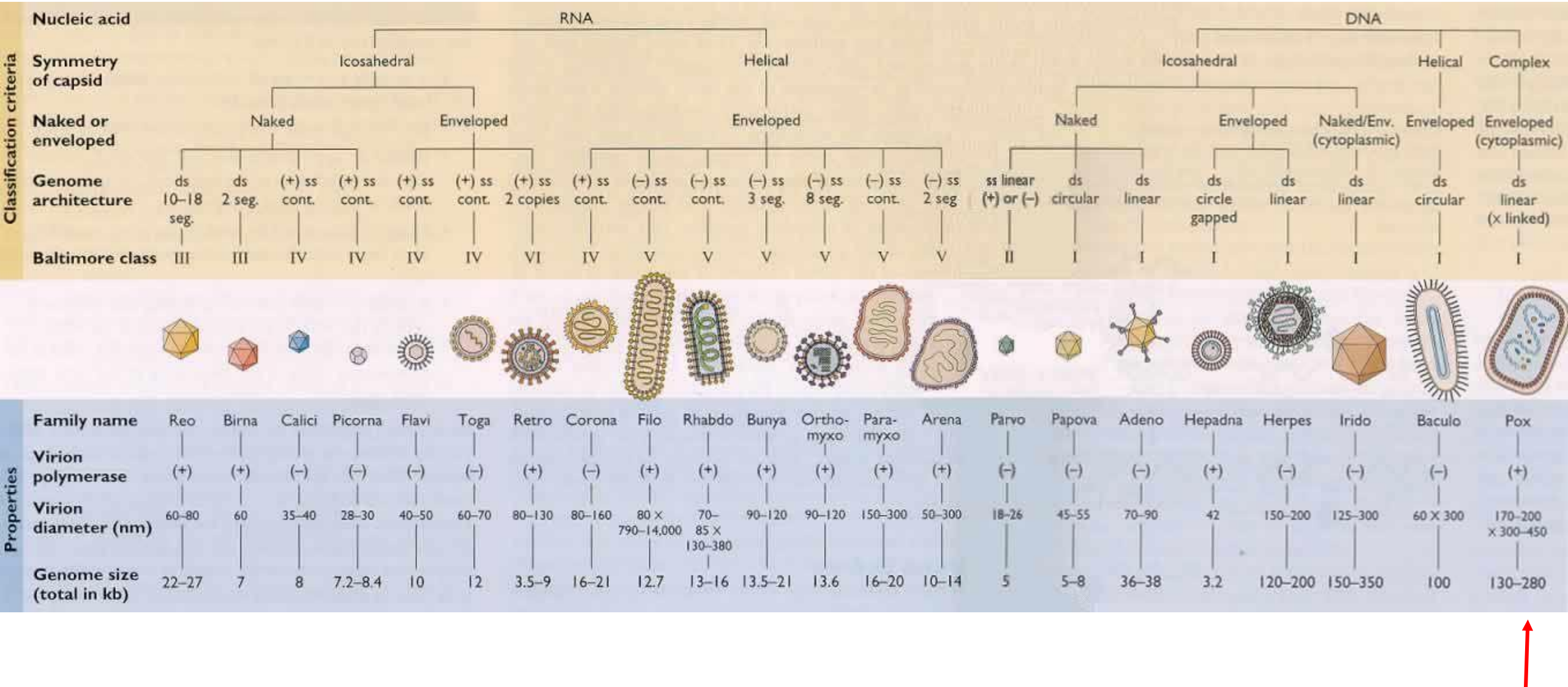
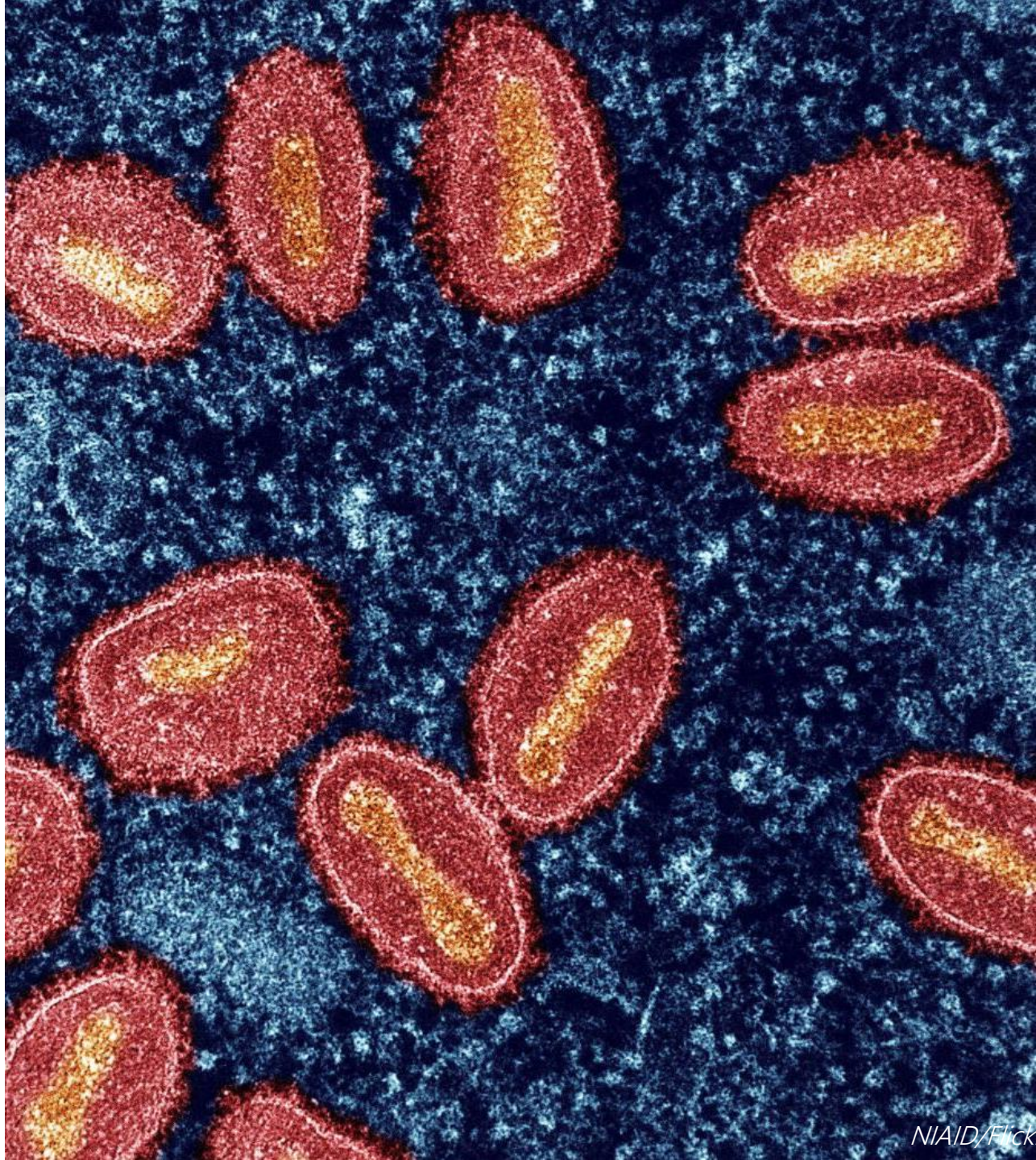
Pox viruses


Classification criteria
Nucleic acid
RNA
DNA
Symmetry of capsid
Icosahedral
Helical
Icosahedral
Helical
Complex
Naked or enveloped
Naked
Enveloped
Enveloped
Naked
Enveloped
Naked/Env. (cytoplasmic)
Enveloped
Enveloped (cytoplasmic)
Genome architecture
ds 10–18 seg.
ds 2 seg.
(+) ss cont.
(+) ss cont.
(+) ss cont.
(+) ss cont.
(+) ss 2 copies
(+) ss cont.
(–) ss cont.
(–) ss cont.
(–) ss 3 seg.
(–) ss 8 seg.
(–) ss cont.
(–) ss 2 seg.
ss linear (+) or (–)
ds circular
ds linear
ds circle gapped
ds linear
ds linear
ds circular
ds linear (× linked)
Baltimore class
III
III
IV
IV
IV
IV
VI
IV
V
V
V
V
V
V
II
I
I
I
I
I
I
I
Properties
Family name
Reo
Birna
Calici
Picorna
Flavi
Toga
Retro
Corona
Filo
Rhabdo
Bunya
Ortho-myxo
Para-myxo
Arena
Parvo
Papova
Adeno
Hepadna
Herpes
Irido
Baculo
Pox
Virion polymerase
(+)
(+)
(–)
(–)
(–)
(–)
(+)
(–)
(+)
(+)
(+)
(+)
(+)
(+)
(–)
(–)
(–)
(+)
(–)
(–)
(–)
(+)
Virion diameter (nm)
60–80
60
35–40
28–30
40–50
60–70
80–130
80–160
80 × 790–14,000
70–85 × 130–380
90–120
90–120
150–300
50–300
18–26
45–55
70–90
42
150–200
125–300
60 × 300
170–200 × 300–450
Genome size (total in kb)
22–27
7
8
7.2–8.4
10
12
3.5–9
16–21
12.7
13–16
13.5–21
13.6
16–20
10–14
5
5–8
36–38
3.2
120–200
150–350
100
130–280

Various pox viruses

Mpox

- Mpox infection is caused by the monkeypox virus (MPXV) of the Orthopoxvirus genus. MPXV is a DNA virus comprising 2 clades
- Clade I (formerly known as Congo Basin clade)
- Clade II (formerly known as West African clade)
  - Further divides into subclades IIa and Iib
- In 2024, a new subclade of Clade I, known as Ib, was identified in the African region



New clade 1b- situation

- According to the Africa CDC Epidemic Intelligence Report issued on 23 August 2024 over 20 000 mpox cases have been reported from 13 African Union Member States so far in 2024, including 3 311 confirmed cases and 582 deaths (case fatality; CF 2.9%).
- Of these, 19 667 cases (16 706 suspected and 2 961 confirmed) including 575 deaths (CF 2.9%) were reported from all provinces in the DRC where MPXV subclade Ia and Ib circulate, representing over 90% of the cases reported on the African continent to date.

- Clade Ia: Republic of the Congo (21 confirmed cases and 141 suspected) and Central African Republic (45 confirmed cases), both of which reported cases in 2023;
- Clade Ib: Burundi (190 confirmed and 512 suspected cases), Rwanda (four confirmed cases), and Uganda (three confirmed cases).
- In addition, Kenya reported one person infected with MPXV clade Ib in 2024 and another where the clade is still unknown, and Gabon reported. one person with mpox on 22 August with travel history to Uganda
- One case of confirmed clade 1 in Sweden Aug 2024

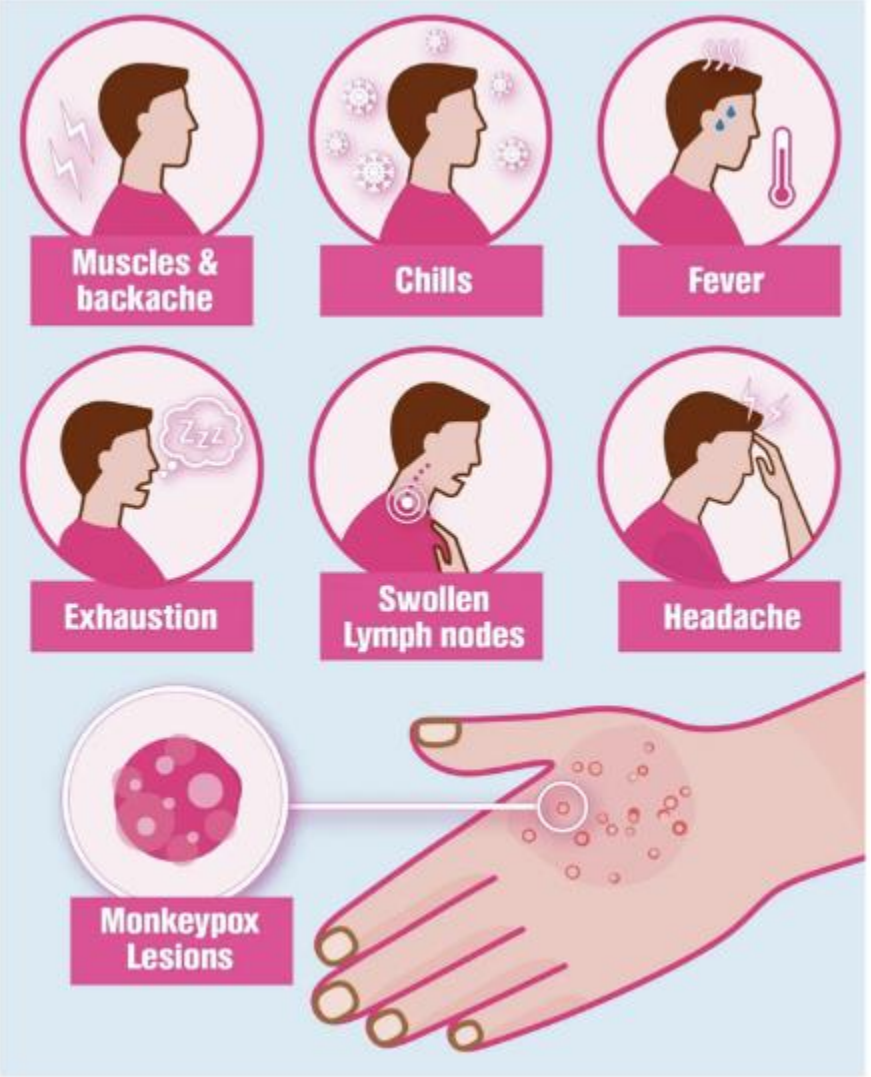
WHO changed the name from Monkeypox to **mpox** on 28 Nov 2022

Table 1. Features of the Classic Form of Monkeypox and the New Clinical–Epidemiologic Form.

Variable	Classic Form, 1970s to the Present	New Clinical–Epidemiologic Form, 2022
Location	Central and West Africa	Countries where monkeypox is not endemic (Europe, North and South America, Middle East, Australia)
Affected population	Children and young adults (age at diagnosis increasing since 1980)	Young men who have sex with men (age, 31–40 yr)
Epidemiologic features	Sporadic cases and epidemics	Pandemic under way since May 2022
Transmission	Contact with infected animal reservoir (probably rodents), followed by human-to-human transmission	Exclusively human-to-human transmission
Dissemination	Mostly intrafamilial and limited nosocomial dissemination	Mostly sexual networking, condomless sex with multiple male partners
Clinical phase	Incubation, prodromal stage, eruption phase with skin lesions	Incubation, prodromal stage (not always present), eruption phase with lesions in an unusual distribution, especially on the genitals
Symptoms	Lesions on the face and extremities, with centrifugal distribution, often associated with cervical or axillary lymphadenopathy	Penile rash, perianal lesions, ulcerative lesions and vesicular rash, painful inguinal lymphadenopathy, pharyngitis, proctitis
Case fatality rate (%)	1–15	0.025

Gessain A, et al. ***N Engl J Med*** *2022;387:1783-93. DOI: 10.1056/NEJMra2208860*

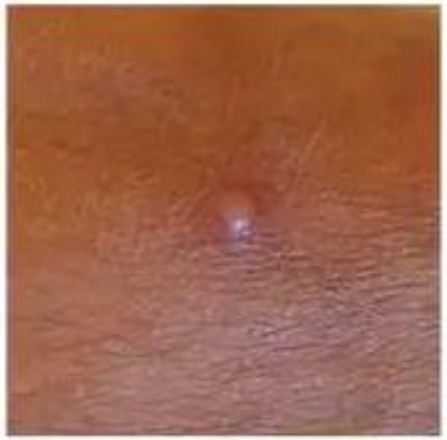
Key Clinical Characteristics for Identification



- **Incubation period:** ~ 7−14d (range 5−21d)
- **First symptoms**: fever, malaise, headache, sometimes sore throat and cough, and lymphadenopathy
- **Lymphadenopathy** ~50%.
  - Occurs with fever onset, **1–2d before rash**, or rarely with rash.
  - Cervical 85.6%, inguinal 77.3%
- Lesions well circumscribed, deep seated, and often **umbilicated**
- Lesions are relatively the **same size & same stage** of development on a **single site of the body** (ex: pustules on face or vesicles on legs)
- Rash is **centrifugal** (more lesions on extremities, face)
- Lesions on **palms, soles** (vs chickenpox)
- **Painful** until the healing phase when they become itchy (crusts)
- **Mucosal lesions 28.7%**: Oral ulcers, Inflammation of the pharyngeal, conjunctival and genital mucosae

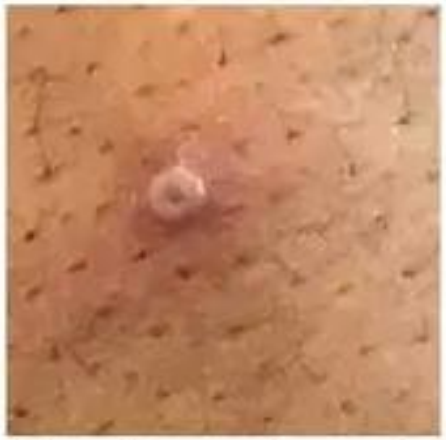
CDC, WHO

Stages of Monkeypox

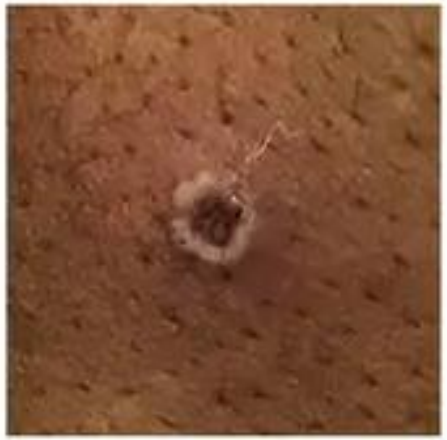


a) early vesicle, 3mm diameter

b) small pustule, 2mm diameter

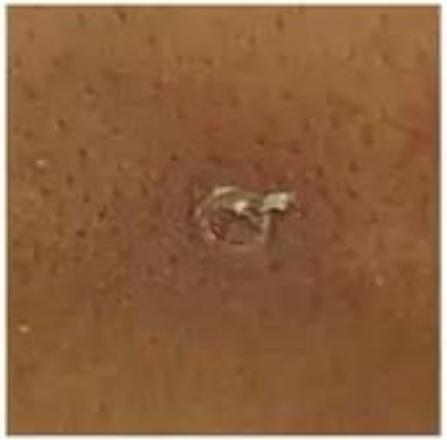


c) umbilicated pustule, 3-4mm diameter



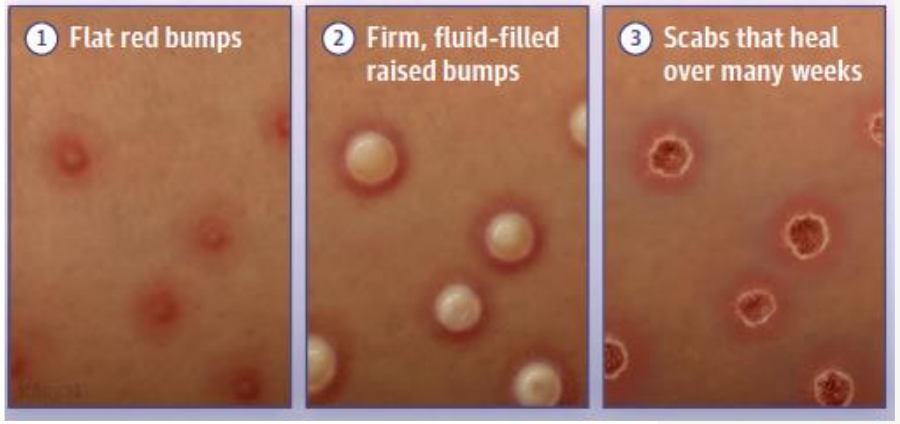
d) ulcerated lesion, 5mm diameter

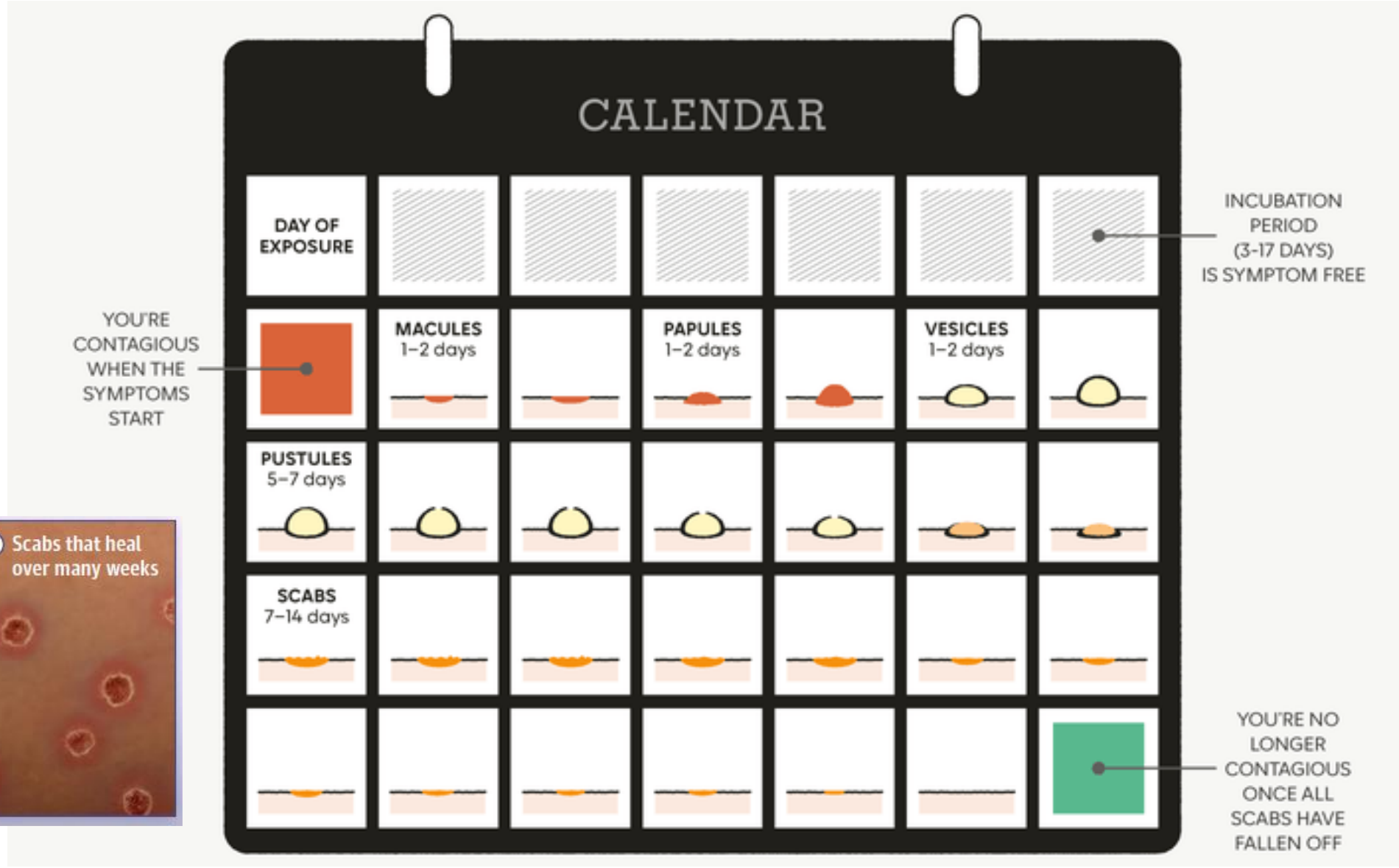
e) crusting of a mature lesion



f) partially removed scab

UK Health Security Agency

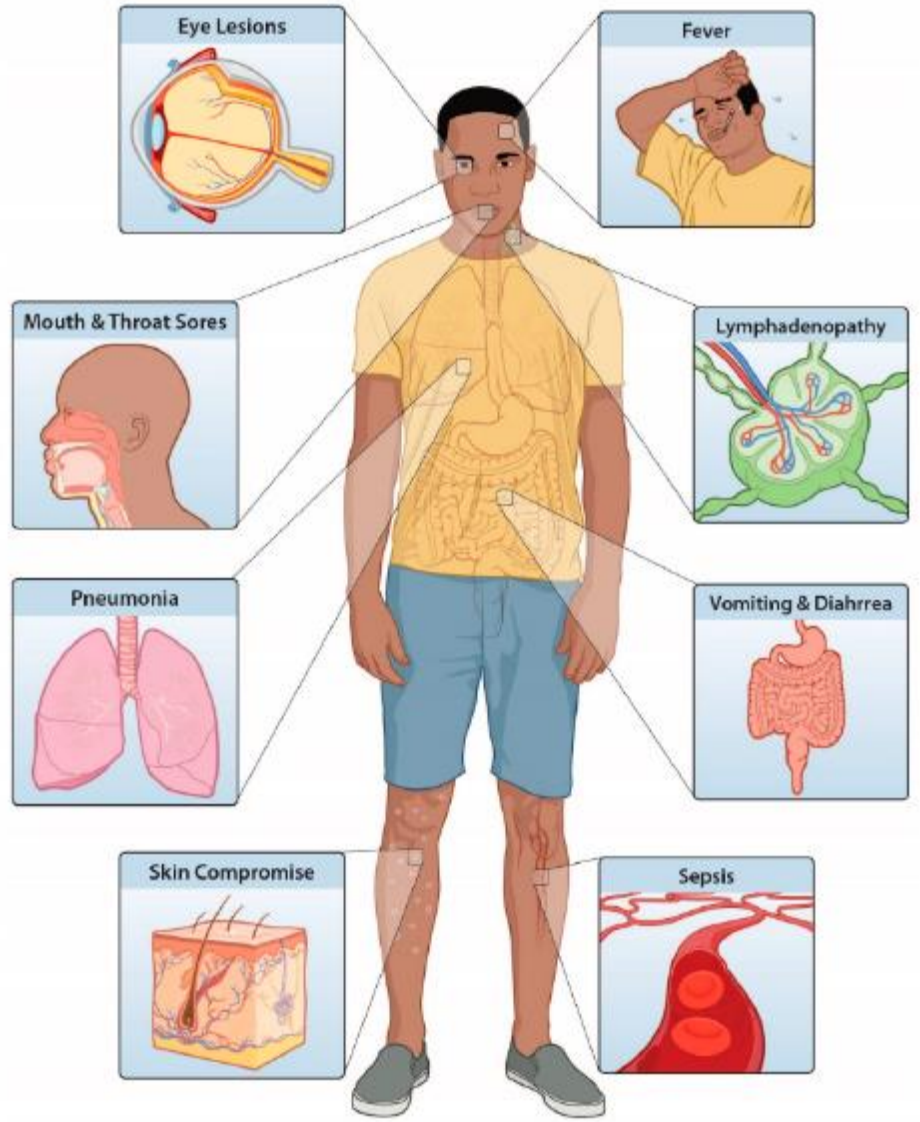




https://www.grxstatic.com/4f3rgqwzdznj/7l8ranOtUMpgO67GGDG1Cn/e89a96a5575dc0c6c26669b0a418085a/monkeypox-a-timeline_goodrx.png?format=png&auto=webp&width=704

Complications of Monkeypox

- **GI:** vomiting and diarrhoea, leading to dehydration & electrolytes imbalance
- **Eye:** conjunctivitis and corneal scarring, leading to blindness
- **Sepsis** from skin or LN infection
- **Encephalitis**
- **Bronchopneumonia**
- Permanent pitted **scarring** secondary to bacterial infection
- **Miscarriage** in pregnant women
- **CFR:** 0-11% in unvaccinated individuals
- **Immunocompromised individuals**, e.g. untreated HIV infections **more serious [illegible] risk of fatality**



Beer EM, et al. ***PLoS Negl Trop Dis.*** *2019 Oct 16;13(10):e0007791*
Reynolds MG, et al. ***Viruses*** *2017 Dec 12;9(12):380.*

CASE RECORDS of the MASSACHUSETTS GENERAL HOSPITAL

Case 24-2022: A 31-Year-Old Man with Perianal and Penile Ulcers, Rectal Pain, and Rash

This article was published on June 15, 2022, at NEJM.org.

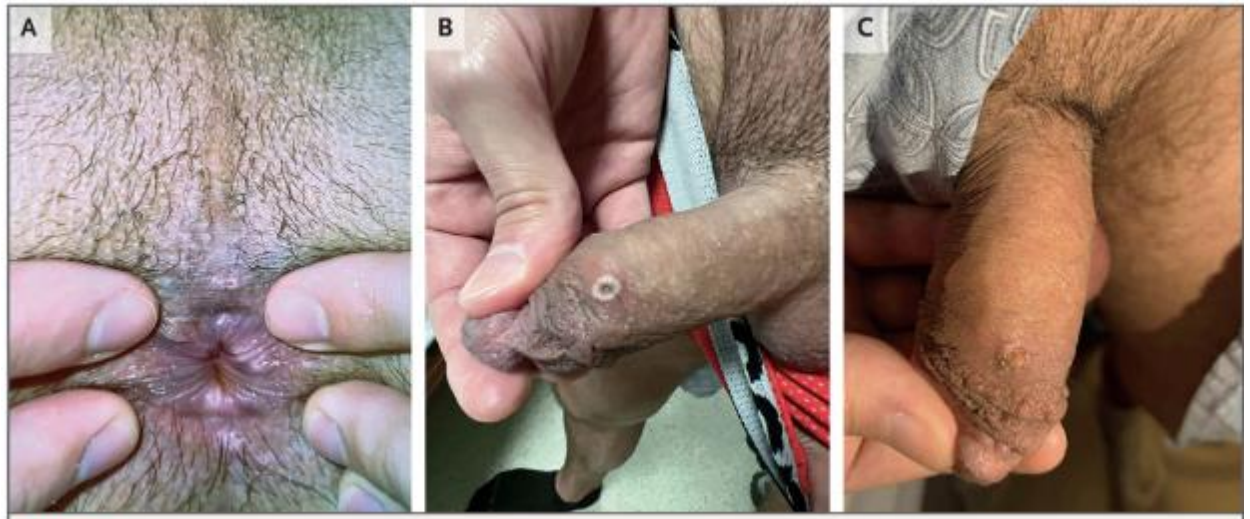
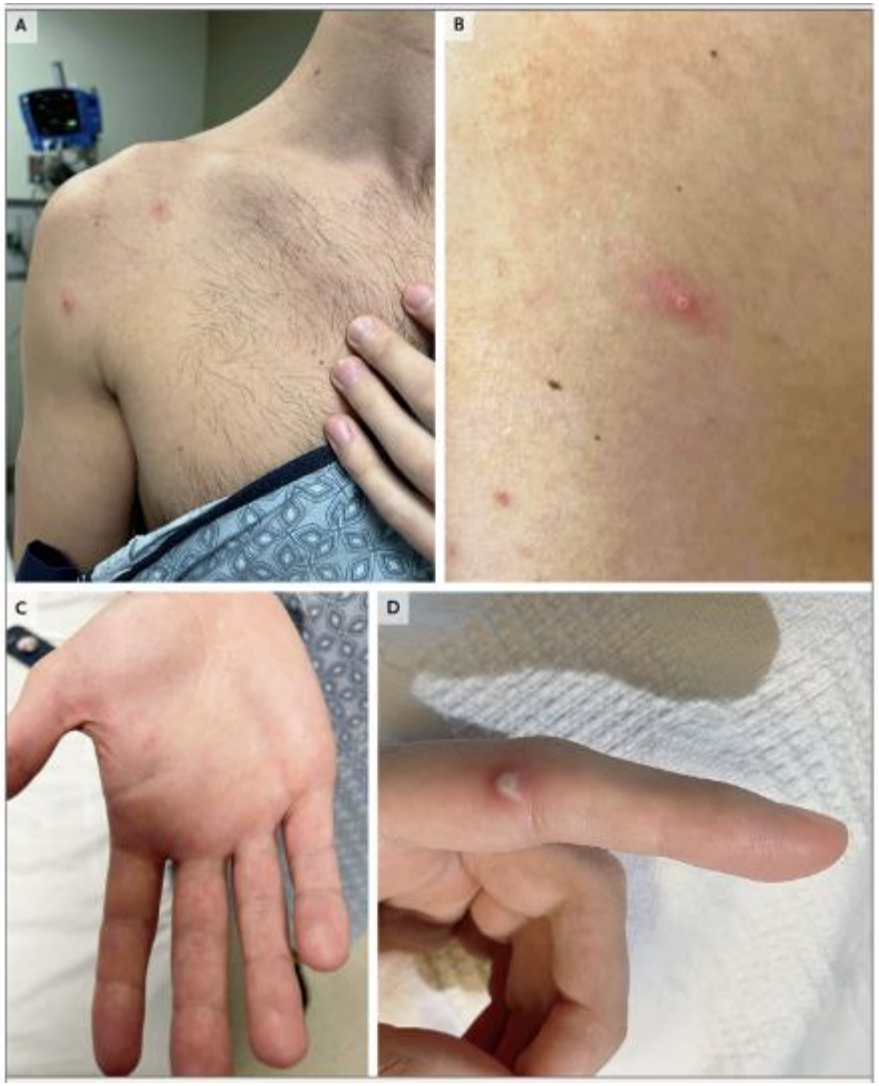


Figure 1. Photographs of Perianal and Penile Ulcers from 2 Days before Admission.

Figure 3. Photograph from Anoscopic Examination.

DDX:

- Viral: HSV, VZV, HIV, molluscum contagiosum
- Bacterial:
  - Gonorrhoea
  - Syphilis
  - LGV
  - Chancroid



Severe Proctocolitis leading to GIB

(Hb dropped from 15 to 7g/dL)

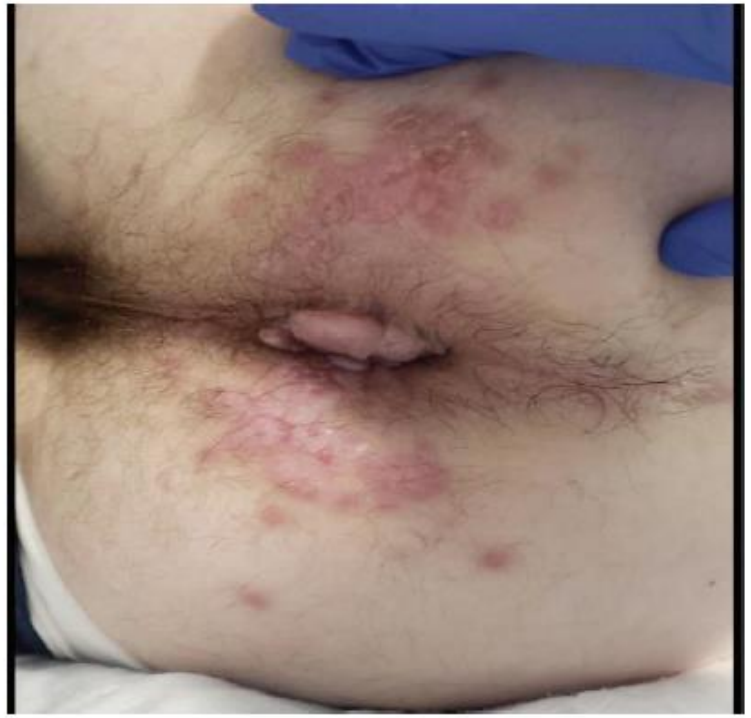


FIGURE 1: Monkeypox-induced perianal lesions. These painful perianal lesions were the initial manifestation of the monkeypox virus infection.

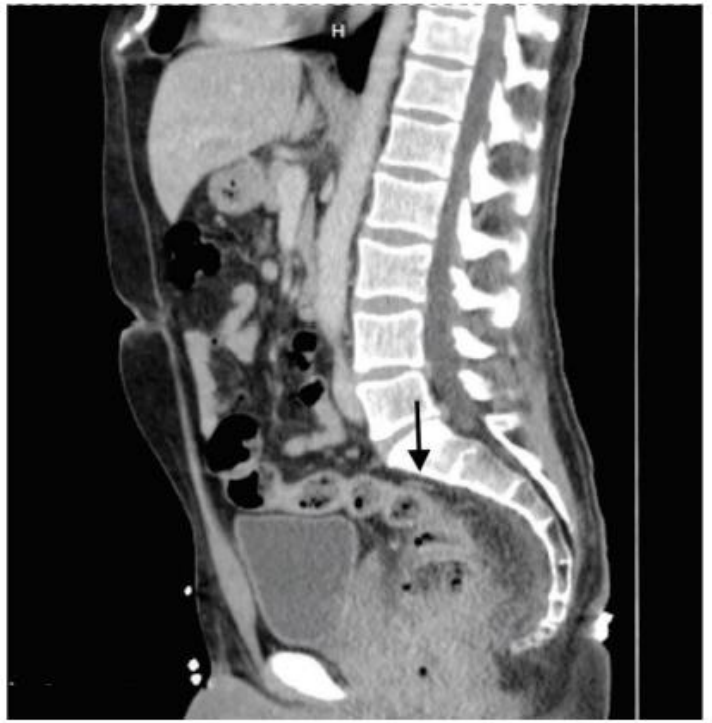
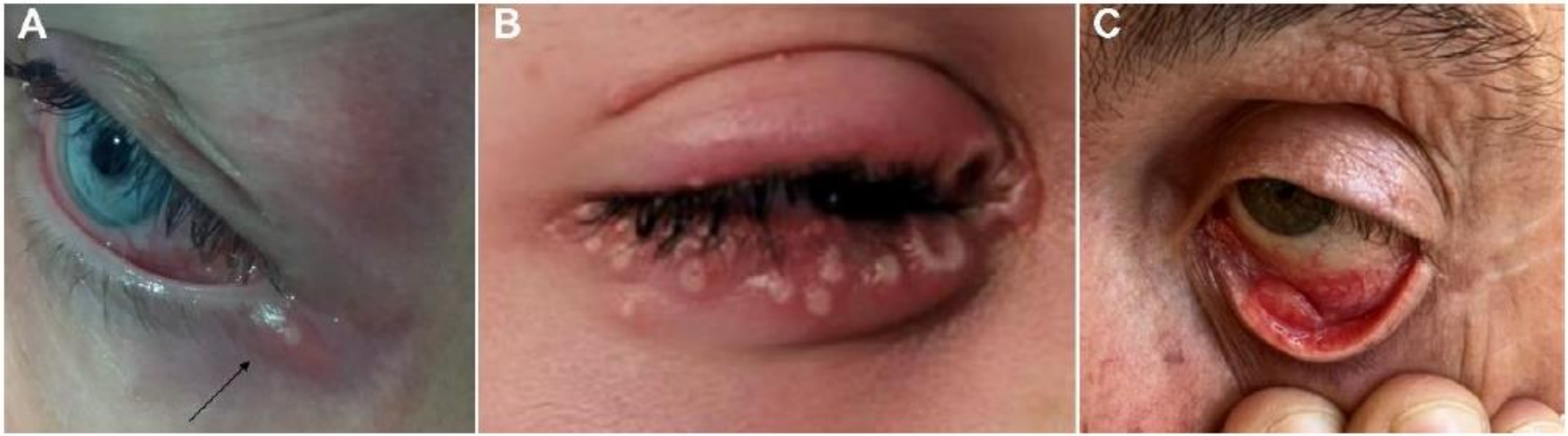


FIGURE 2: CT angiography (CTA) of the abdomen and pelvis. CT angiography revealed circumferential wall thickening with significant inflammatory changes at the level of the distal rectum and anus, indicating proctocolitis (black arrow). Small rounded hypodensities, adjacent to the distal rectum measuring 11 and 14 mm, were suspicious for rectal abscesses.

Taj S, et al. ***Case Rep Gastrointest Med*** *2023, 9981631.*

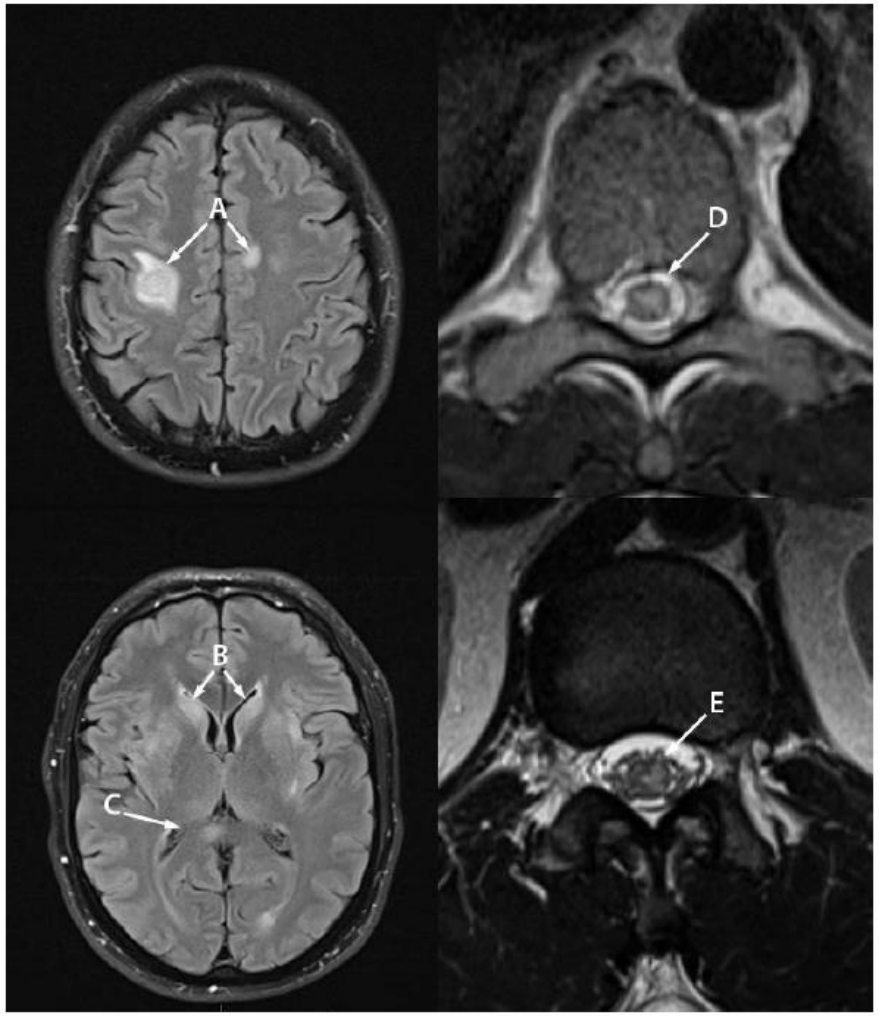
Eye lesions

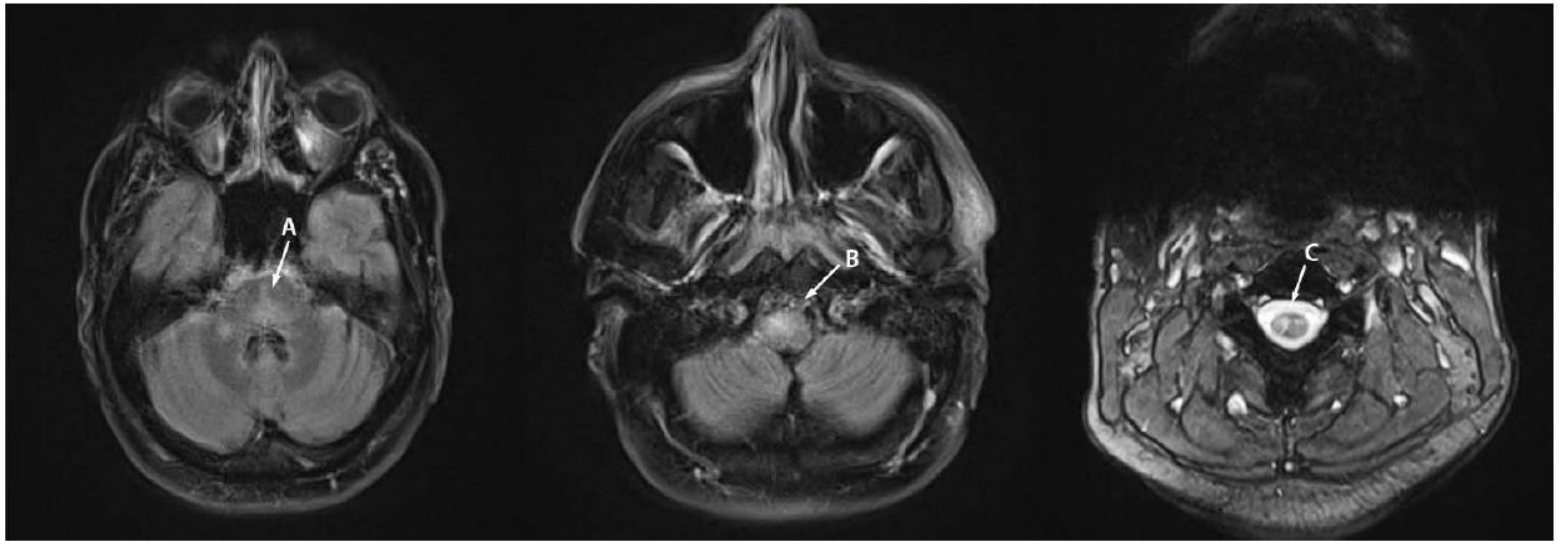


(A) Vesicles on the left lower eyelid (black arrow).
(B) Multiple papular lesions on the right eyelid.
(C) Ulceration of the palpebral conjunctiva

Zong Y, et al. ***Viruses*** *2023, 15, 616.*

CNS encephalomyelitis





Abnormal T2/fluid attenuated signal in:

(A) right frontal and left frontal lobes
(B) bilateral basal ganglia
(C) bilateral medial thalami and right splenium
(D) central thoracic spinal cord
(E) gray matter of the conus medullaris

Abnormal T2/fluid attenuated signal in:

(A) pons and cerebellum
(B) Medulla
(C) gray matter of the cervical spinal cord

Pastula DM, et al. ***MMWR Morb Mortal Wkly Rep.*** *2022 Sep 23;71(38):1212-1215.*

Differential diagnosis

- Chickenpox
- HSV
- Primary or secondary syphilis
- Disseminated gonococcal infection
- Hand, foot and mouth disease
- Chancroid
- Lymphogranuloma venereum
- Granuloma inguinale
- Molluscum contagiosum, measles, scabies, Rickettsia pox
- Chikungunya, zika virus, dengue fever
- Vasculitis and other bacterial skin and soft tissue infections

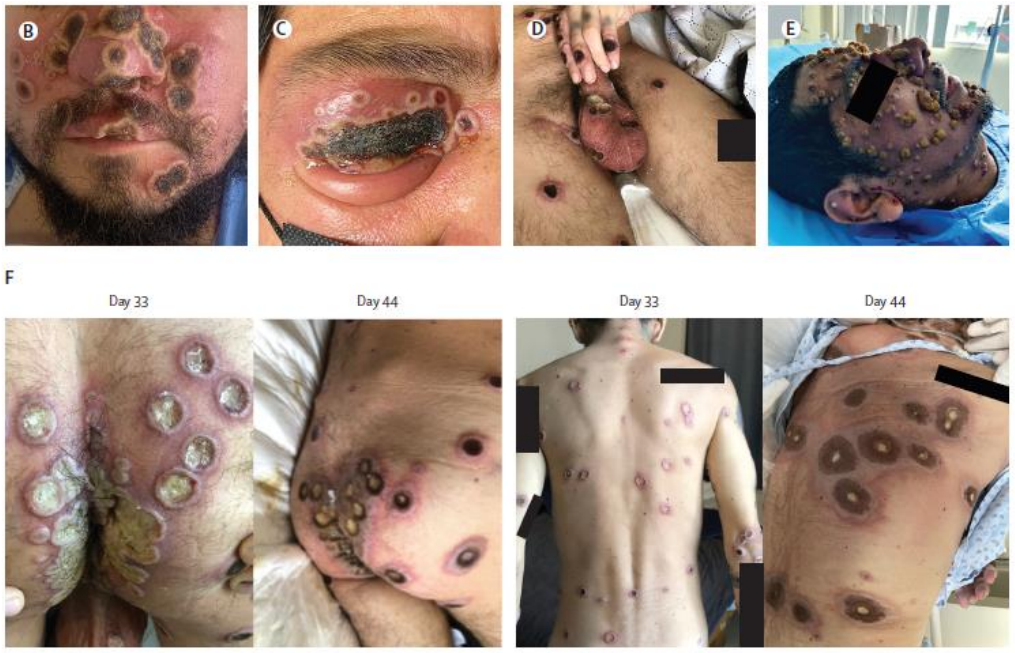
Variable	Monkeypox	Smallpox	Chickenpox
Time period (days)			
Incubation stage	7–17	7–17	10–21
Prodromal stage	1–4	1–4	0–2
Illness stage (from the appearance of rashes to desquamation)	14–28	14–28	10–21
Severity of symptoms			
Prodromal fever	Moderate	Severe	None or mild
Fever	Moderate	Severe	Mild
Malaise	Moderate	Moderate	Mild
Headache	Moderate	Severe	Mild
Lymphadenopathy	Moderate	None	None
Lesions			
Distribution	Centrifugal	Centrifugal	Centripetal
Frequency of lesions on the palms or soles	Common	Common	Rare
Appearance	Hard, well-circumscribed, umbilicated	Hard, well-circumscribed, umbilicated	Superficial, irregular borders, "dew drop on a rose petal"
Depth (diameter in mm)	Deep (4–6)	Deep (4–6)	Superficial (2–4)
Evaluation	Homogenous	Homogenous	Heterogeneous
Progression	Slow progression with each stage lasting 1–2 days	Slow progression with each stage lasting 1–2 days	Fast progression
Extracutaneous manifestations			
Secondary skin/soft-tissue infection	19%	Possible	Possible
Pneumonitis	12%	Possible	3–16%
Ocular complications	4–5%	5–9%	No
Encephalitis	<1%	<1%	<1%

Zahmatyar M, et al. ***Front Med*** *2023;10:1157670*

Centrifugal distribution

Petersen E, et la. ***Infect Dis Clin North Am.*** *2019 Dec;33(4):1027-1043*

MPOX in HIV



HIV with CD4 < 200 cells/mL has more:

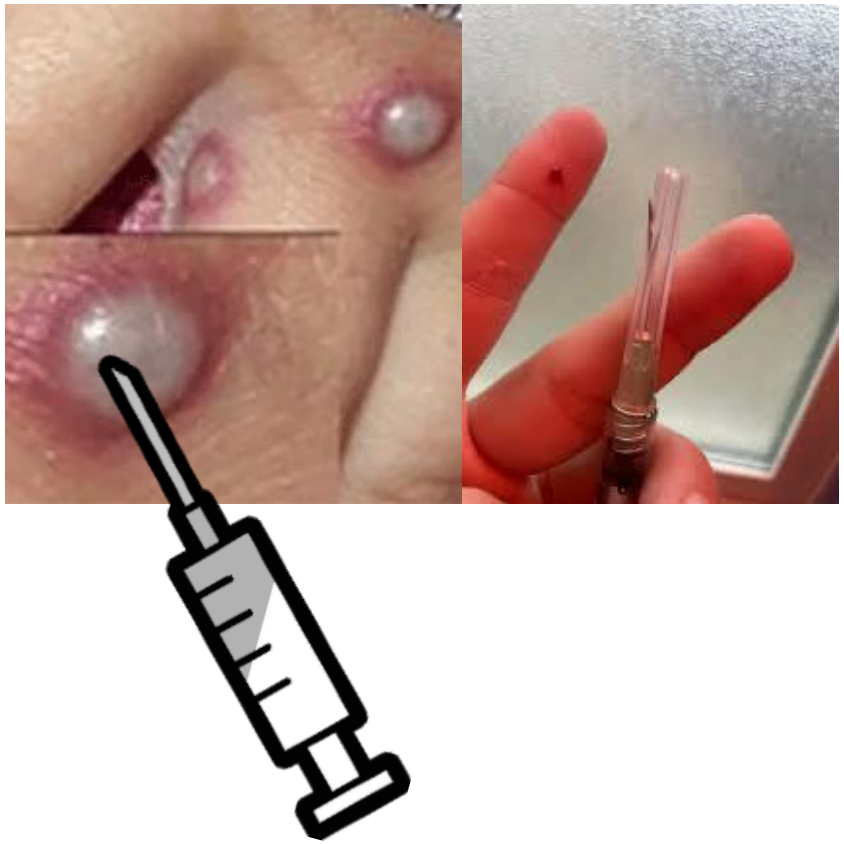
- Longer course of diseases
- Fulminant disseminated necrotizing cutaneous lesions
- Systemic diseases
- Higher mortality

Mitja O, et al. ***Lancet*** *2023; 401: 939–49*

	Total (n=382)	CD4 <100 cells per mm³* (n=85)	CD4 100–200 cells per mm³ (n=94)	CD4 201–300 cells per mm³ (n=128)	CD4 >300 cells per mm³ (n=75)
Mpox rash presentation					
Peak number of skin lesions	15 (8–35)	30 (15–100)	20 (12–35)	12 (6–20)	10 (4–15)
Rash duration in days	23 (18–33)	31 (21–45)	26 (19–40)	21 (16–28)	21 (15–30)
Mpox organ complications†					
Dermatological skin lesions distant from the point of entry					
Overall	94 (25%)	49 (58%)	20 (21%)	18 (14%)	7 (9%)
Large necrotising lesions	84 (22%)	46 (54%)	19 (20%)	14 (11%)	5 (7%)
Ecchymosis haemorrhage	10 (3%)	3 (4%)	1 (1%)	4 (3%)	2 (3%)
Respiratory					
Overall	35 (9%)	25 (29%)	5 (5%)	5 (4%)	0
CNS					
Overall	12 (3%)	9 (11%)	1 (1%)	0	1 (1%)
Ultimate Outcome					
Death§	27 (7%)	23 (27%)	4 (4%)	0	0
Organ support					
Need for ventilation	21 (5%)	16 (19%)	4 (4%)	1 (1%)	0
Need for inotropes	16 (4%)	13 (15%)	3 (3%)	0	0
Indication for ventilation					
Respiratory failure	17 (4%)	14 (16%)	2 (2%)	1 (1%)	0
Sedation	1 (0%)	0	1 (1%)	0	0
Low Glasgow Coma Score or coma	3 (1%)	2 (2%)	1 (1%)	0	0

Morbidity and Mortality Weekly Report

Monkeypox Virus Infection Resulting from an Occupational Needlestick — Florida, 2022



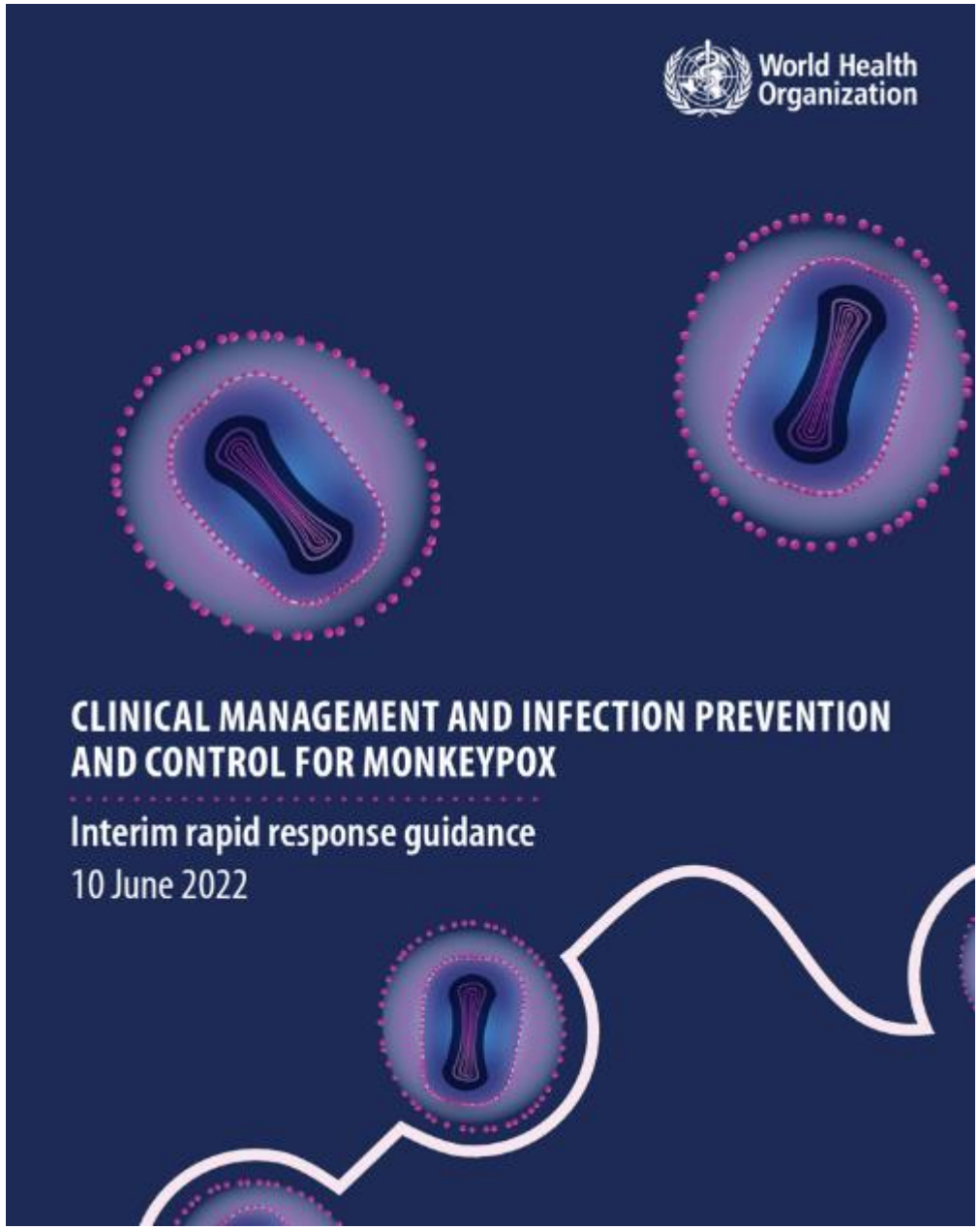
- A nurse used a needle to puncture the vesicle to facilitate swabbing
- NSI occurred when recapping with small amount of bleeding.
- Immediately washed with soap and water and drenched with Betadine antiseptic solution (10% povidone-iodine).
- Received 1st dose of JYNNEOS vaccine 15 hours after the incident as PEP
- 10 days after the exposure, a single skin lesion formed at the site of the needlestick.
- Swabbed +ve for MPOX
- ↑ in size but < 1cm. Then crusted & fallen off 19 days later.
- No additional lesions
- No Rx given

Conclusion:

- NSI can transmitted MPOX
- PEP is effective

Mendoza R, et al. ***MMWR Morb Mortal Wkly Rep****. 2022 Oct 21;71(42):1348-1349. doi: 10.15585/mmwr.mm7142e2.*

Management of Monkeypox



Management

- Aim: prevent complication, relieve discomfort, speed healing
- Support care
- Prevent secondary bacterial infection
- Pain relief
- Nutritional support
- Adequate hydration
- Symptomatic treatment
- Monitoring
- Antivirals for severe diseases

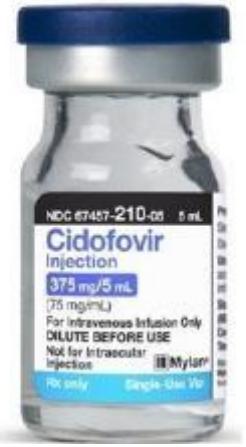
WHO. ***CLINICAL MANAGEMENT AND INFECTION PREVENTION AND CONTROL FOR MONKEYPOX*** *Interim rapid response guidance* ***10 June 2022***

Table 3.1. Risk factors and clinical findings described as being associated with severe disease and poor outcomes (based on small, uncontrolled, observational studies)

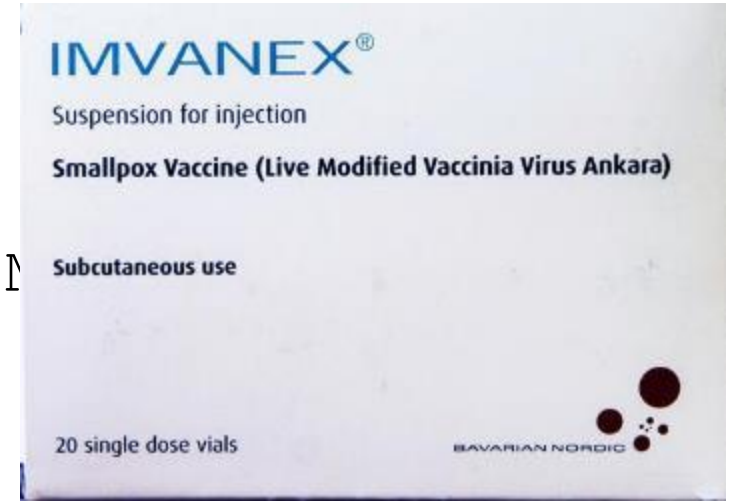
Patient groups at higher risk of severe disease or complications	• Children, pregnant women, persons who are immunosuppressed such as persons living with HIV having poorly controlled disease *(5,6,10,11,13,26)*. • Though data are lacking, patients with chronic skin conditions (e.g. atopic dermatitis), acute skin conditions (i.e. burns) may also be at higher risk for complications, such as bacterial infection *(33)*.
Clinical signs and symptoms of complications	• Nausea and vomiting *(11,16)*, painful cervical lymphadenopathy causing dysphagia, poor oral intake, eye pain, vision abnormalities, hepatomegaly, sepsis, dehydration, respiratory distress/pneumonia, and/or confusion.
Laboratory abnormalities	• Elevated hepatic transaminases (AST and/or ALT), low blood urea nitrogen (BUN), low albumin, elevated white blood count (WBC), or low platelet count *(16)*.
Skin lesion severity score	• From smallpox experience *(28,94)*: – Mild (< 25 skin lesions) – Moderate (25–99 skin lesions) – Severe (100–250 skin lesions) – Very severe (> 250 skin lesions).

Antivirals and vaccines

- **Treatment**
  - Tecovirimat
  - Brincidofovir
  - Cidofovir
  - Vaccinia Immune Globulin Intravenous (VIGIV)



- **Vaccines**
  - JYNNEOS (Imvamune, Imvanex or N
  - ACAM2000



Antivirals vs MPOX

Table 1 - General characteristics of tecovirimat, cidofovir and brincidofovir.

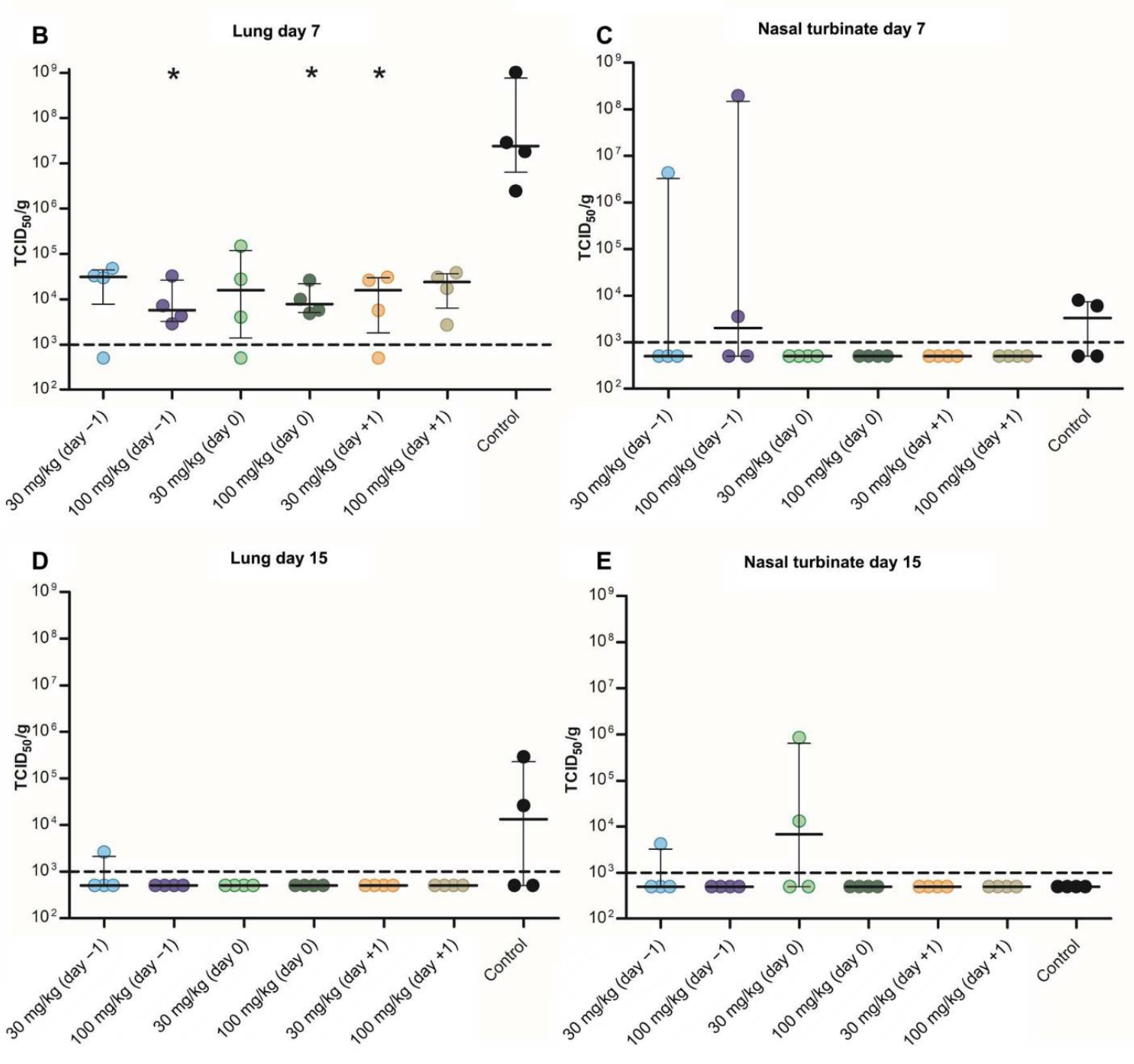
	Tecovirimat	*Cidofovir*	*Brincidofovir*
Mechanism of action	Inhibitor of the Orthopoxvirus VP37 envelope wrapping protein	DNA polymerase inhibitor	DNA polymerase inhibitor
EMA approval	Poxviridae Infections, Smallpox Cowpox, Vaccinia Monkeypox	No	No - Orphan drug designation
FDA approval	Smallpox	CMV retinitis	Smallpox
Dosing	PO: 13 kg-24 kg: 200 mg bid; 25 kg-40 kg: 400 mg bid; >40 kg: 600 mg bid; IV: 3kg-35 kg: 6 mg/kg bid over 6 hours; 35 kg-120kg: 200 mg bid over 6 hours; >120 kg: 300 mg bid over 6 hours	PO: Not available IV: 5 mg/kg once weekly	PO: <10 kg: 6 mg/kg/dose once weekly in 2 doses (on days 1 and 8); 10 kg - 48 kg: 4 mg/kg once weekly for 2 doses (on days 1 and 8); >48 kg: 200 mg once weekly for 2 doses (on days 1 and 8) IV: Not available
Course duration	14 days	2 consecutive weeks	2 consecutive weeks
Renal toxicity	IV Tecovirimat is contraindicated if CrCl < 30 mL/min	Possible. Adjust dose accordingly	No
Hepatic toxicity	No	No	Possible. Adjust dose accordingly

Abbreviations: PO, per os (by mouth); bid, bis in die (twice daily); IV, intravenous; CrCl, creatinine clearance.

*Ivanov DT, et al. **Infez Med**. 2023 Jun 1;31(2):186-194.*

Tecovirimat: mice study

- Mice were given 2 doses of Tecovirimat:
  - 30mg/kg or
  - 100mg/kg
- Rx given at D-1, D0 or D+1 of viral inoculation x 5d
- Measure viral loads at D7 or D15 after Rx
- Vs control



Warner, BM, et al. ***Sci Transl Med.*** *2022 Nov 30;14(673):eade7646.*

Efficacy of Tecovirimat

- Case series in Germany[1]:
  - All 12 cases showed clinical improvement
- Case series in US[2]:
  - 2 cases showed resolution of lesions after prolonged Rx
  - 6 cases showed resolution of lesions after 14d Rx

- Cases control study[3]:
  - 19 Rx vs 22 Un-Rx
  - No significant changes in clinical recovery and viral loads after 14d Rx

1. *Hermanussen L, et al.* ***Infection****. 2023 Oct;51(5):1563-1568.*
2. *Seifu L, et al.* ***MMWR Morb Mortal Wkly Rep****. 2023 Apr 28;72(17):471-472.*
3. *Mazzotta V, et al****. J Med Virol.*** *2023;95:e28868.*

Tecovirimat for mpox

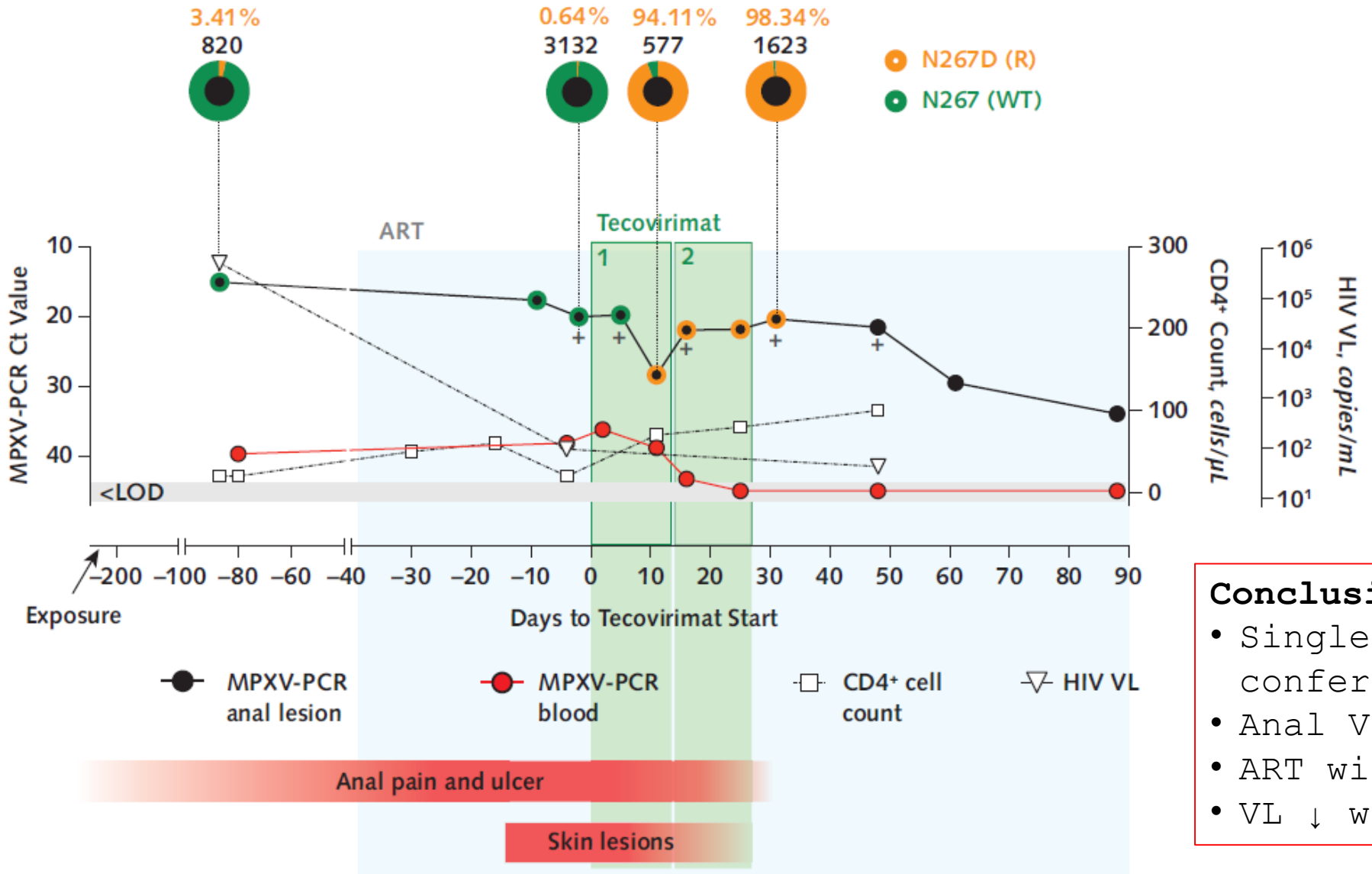
- 369 outpatients given Tecovirimat
- 99.8% oral tecovirimat
- 46.3% HIV +ve
- Median time from initiation of tecovirimat to improvement: **3 days**
- Adverse events **3.5%:** headache (3), nausea (2), visual disturbance (2), weakness (2), vomiting (1), ↑ALT (1), psychiatric admission (1), rash (1), hives (1), numbness (1), fatigue (1), and dizziness (1).

Outcome (no. unknown or missing)	No. (%)
Hospitalized (38)	
Yes*	23 (6.9)
Intensive care unit*	2 (0.6)
No	308 (93.1)
Outcome† (52)	
Recovered without sequelae	189 (59.6)
Recovered with sequelae	41 (12.9)
Not yet recovered	87 (27.4)
Days to subjective improvement§ (114)	
Median, days (IQR)	3.0 (2–4)
Adverse event¶ (29)	
Yes	12 (3.5)
No	328 (96.5)

Median no. of days to follow up after treatment initiation (IQR)**	
During treatment: assessment A (day 1–7)	6 (4–7)
During treatment: assessment B (day 8–14)	10 (8–13)
Posttreatment: assessment C	21 (20–23)
Assessment A (day 1–7) (156)	213 (57.7)
New lesions (22)	
Yes	25 (13.1)
No	166 (86.9)
All lesions crusted and healed with new layer of skin (59)	
Yes	49 (31.8)
No	105 (68.2)
Assessment B (day 8–14) (187)	182 (49.3)
New lesions (19)	
Yes	22 (13.5)
No	141 (86.5)
All lesions crusted and healed with new layer of skin (25)	
Yes	78 (49.7)
No	79 (50.3)
Assessment C (posttreatment) (225)	144 (39.0)
New lesions (7)	
Yes	3 (2.2)
No	134 (97.8)
All lesions crusted and healed with new layer of skin (11)	
Yes	119 (89.5)
No	14 (10.5)

O'Laughlin K , et al. ***MMWR Morb Mortal Wkly Rep****. 2022 Sep 16;71(37):1190-1195.*

Tecovirimat resistance: N267D



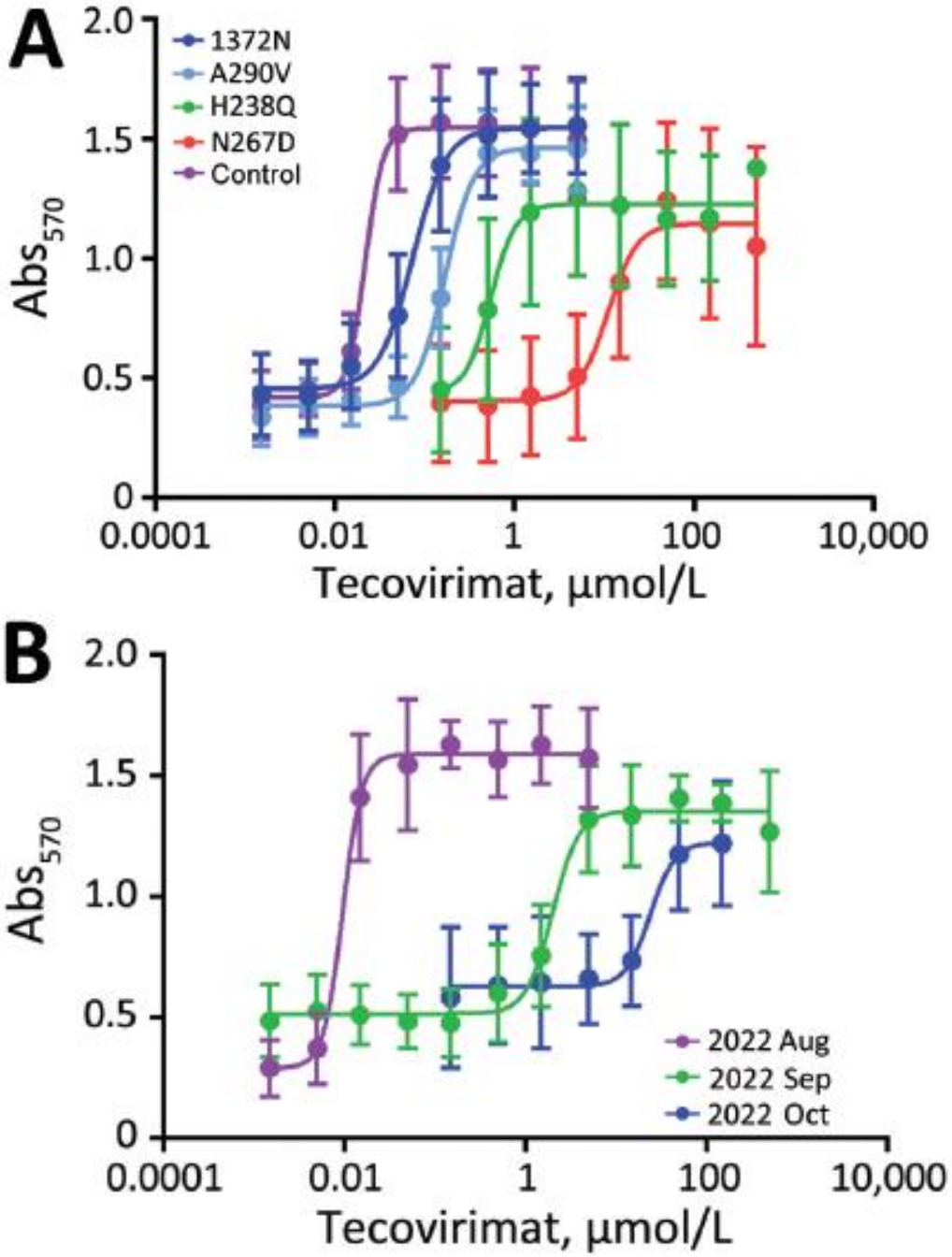
Conclusion:

- Single point mutation N267D confers Teco resistance
- Anal VL > Blood VL
- ART will ↑ CD4
- VL ↓ with ↑ CD4

Mertes H, et al. ***Ann Intern Med.*** *2023*

Tecovirimat resistance

- Envelop protein VP37 mutations associated with Tecovirimat resistance:
  - prior studies: H238Q, P243S, **N267D**, A288P, A290V, D294V, A295E & I372N
  - 5 more new mutations T220A/I, T245I, A265D, and T289A
- Tecovirimat resistance **↑ over time**
- **Single amino acid mutation** can confer resistance



Garrigues JM, et al. ***Antimicrob Agents Chemother.*** *18;67(7):e0056823.*

Summary

- Mpox has been circulating since 1970
- 2022 outbreak is likely related to the transmission within a defined group, but there is outbreak of new clade Ib in African countries
- Sexual transmission is possible besides other common routes
- Atypical presentation includes genital lesions & proctitis with mild or no prodrome
- But severe complications may involve the eyes and the brain
- Antivirals include Tecovirimat, Brincidofovir & cidofovir can be used.
- Antiviral resistance may be an issue
- Smallpox vaccines can help to protect Mpox
- Suspected higher transmission rates and severity among new clade 1b patients

Thank you

Slide credit and gratitude
to Dr Owen Tsang