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New Pox on the Block: Understanding Monkeypox

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Conflict of Interest

- No relevant conflicts of interest to disclose

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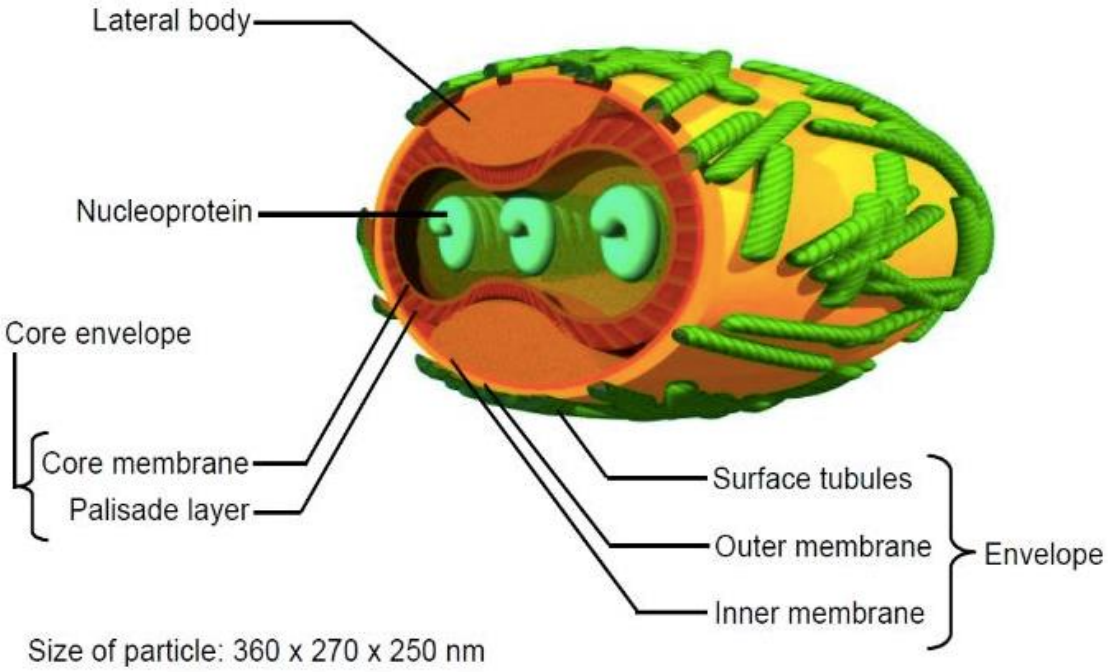
Objectives

1. To understand the history of poxviruses
2. To discuss the epidemiology and pathophysiology of monkeypox virus (MPXV)
3. To review the clinical presentation and diagnosis of MPXV
4. To learn the role of clinical therapeutics and review pertinent data
5. To discuss various preventative strategies

Background – Poxviruses

- Brick-shaped or ovoid enveloped viruses with linear dsDNA[1]
- Considered zoonotic pathogens[2]
- Belong to the *Poxviridae* family
    1. Subfamily – *Entomopoxvirinae*
    2. Subfamily – *Chordopoxvirinae*
        a) 18 genera



[1] *Viruses*. 2021;13(1):43.
[2] *Wilderness Environ Med*. 2021;32(4):528-36.

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Background – Orthopoxviruses

- Most important and well-described poxvirus genus[1]
    a) Smallpox
- Named from the host in which they were originally identified/isolated
- General transmission varies:
    a) Humans vs. animals
    b) Local vs. systemic infection
- New species are still being discovered[2]

[1] *Viruses*. 2021;13(1):43.
[2] *Viruses*. 2019;11(8):708.

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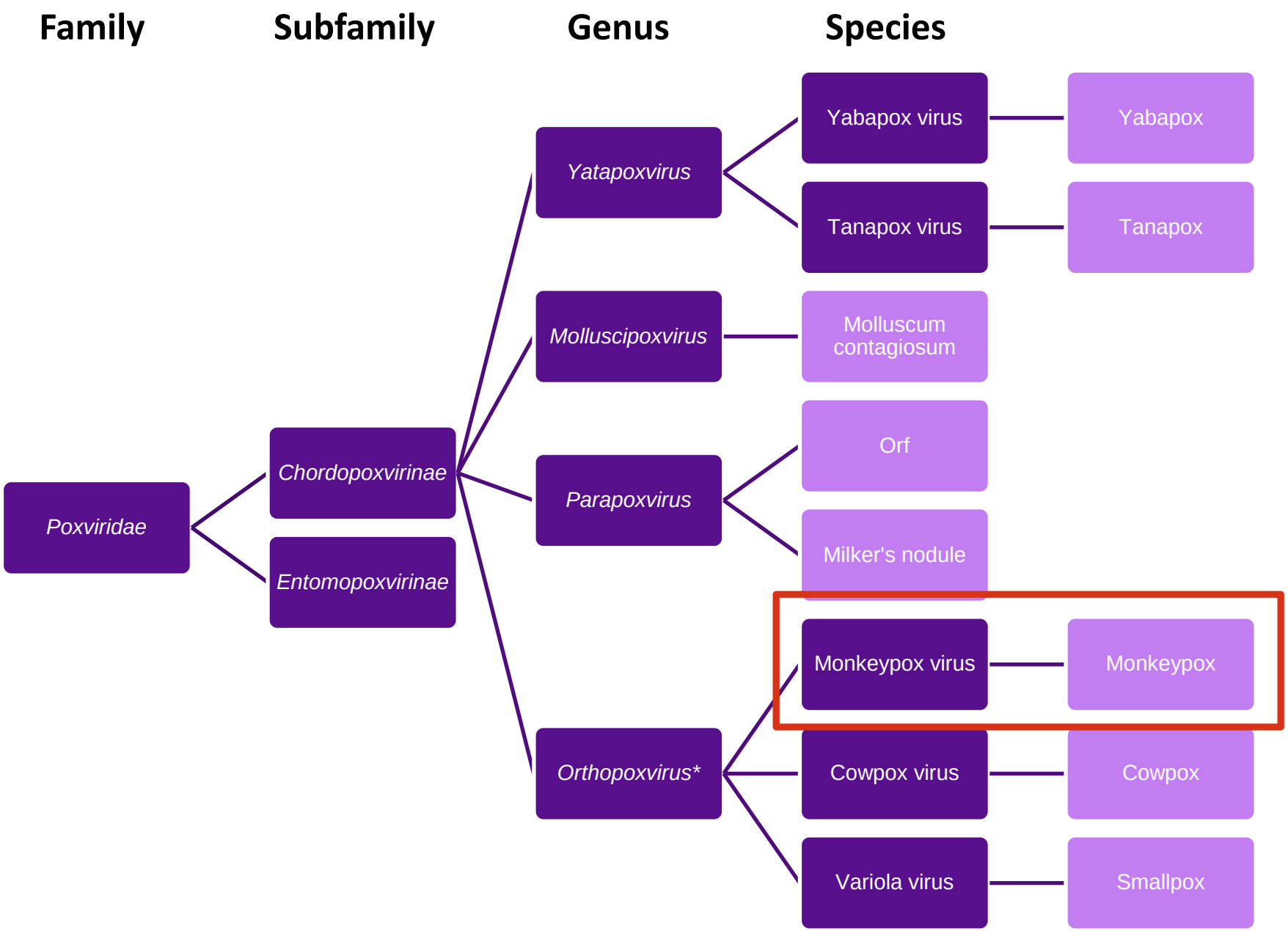

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Monkeypox – Epidemiology

- Natural host unknown – virus isolated twice in wild animals
    a) Infections have been documented in various rodents, primates
- **First MPXV infection reported in 1958[1]**
- **First human infection occurred in 1970[1]**
- Naturally occurring infections typically confined to forested regions of Western and Central Africa[2]
    a) Clade I – Central Africa (i.e. Congo Basin)
    b) Clade II – Western Africa

[1] *Viruses*. 2021;13(1):43.
[2] *Virology*. 2005;341(1):46-63.

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Monkeypox – Epidemiology

- Imported cases rare prior to 2022[1,2]
  a) United States:
     i. **2003 outbreak***
     ii. 2021: TX, MD – 2 cases
  b) United Kingdom, 2018 – 2021 – 7 cases
  c) Israel, 2018 – 1 case
  d) Singapore, 2019 – 1 case

[1] *Viruses*. 2021;13(1):43.
[2] Past U.S. Cases and Outbreaks. CDC. 2022.

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Monkeypox – Epidemiology

- Mortality associated with MPXV varies
  a) Upwards of 17% in the mid-late 1900's[1]
  b) **Clade I > clade II**[2]
     i. Approx. 10% in Central Africa
  c) 2022 outbreak: **first deaths in non-endemic countries**

[1] *Bull World Health Organ*. 1980;58(2):165.
[2] *PLoS Negl Trop Dis*. 2022;16(2):e0010141.

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Monkeypox – Transmission

- Animal-to-human transmission[1]
- Human-to-human less efficient vs. smallpox[2]
  a) Direct contact w/infectious sores, scabs, bodily fluid(s)***
  b) Respiratory secretions – **uncommon**
  c) Fomites
  d) ?Microabrasions of mucous membranes
  e) ?Spread via semen or vaginal fluid[3]
  f) Vertical transmission

[1] *Wilderness Environ Med*. 2021;32(4):528-36.
[2] Clinician Outreach and Communication Activity. May 2022. CDC.
[3] *Euro Surveill*. 2022;27(22):2200421.

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Monkeypox – 2003 U.S. Outbreak

- First reported outbreak in Western hemisphere[1]
- 71 cases across six midwestern states: IL, IN, KS, MO, OH, WI[2]
  a) Traced to imported Gambian pouched rats; prairie dogs
  b) Febrile illness w/pustular rash
  c) 55% (n=39) female; median age 28 (1-51) 26% (n=18) required hospitalization[3]
  d) Median incubation period 12 (1-31) days[3]
  e) **No deaths reported** – resembles clade II[2]
  f) **No documented human-human transmission**

[1] *N Engl J Med*. 2004;350(4):342-50.
[2] *Viruses*. 2021;13(1):43.
[3] *Wilderness Environ Med*. 2021;32(4):528-36.

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Monkeypox – 2022 Outbreak

- May 2022 – first reported cases in the United Kingdom
- First confirmed case in the U.S. – May 17th, 2022[1,2]
    a) Increased mutations, ?accelerated human adaptation?
    b) **Clade IIb**
- July 2022 – declared public health emergency of international concern
- Risk factors: MSM, close contact

[1] *N Engl J Med*. 2022; doi: 10.1056/NEJMcpc2201244.
[2] *MMWR Morb Mortal Wkly Rep*. 2022;71(23):764.
[3] *Nat Med*. 2022; doi: 10.1038/s41591-022-01907-y.

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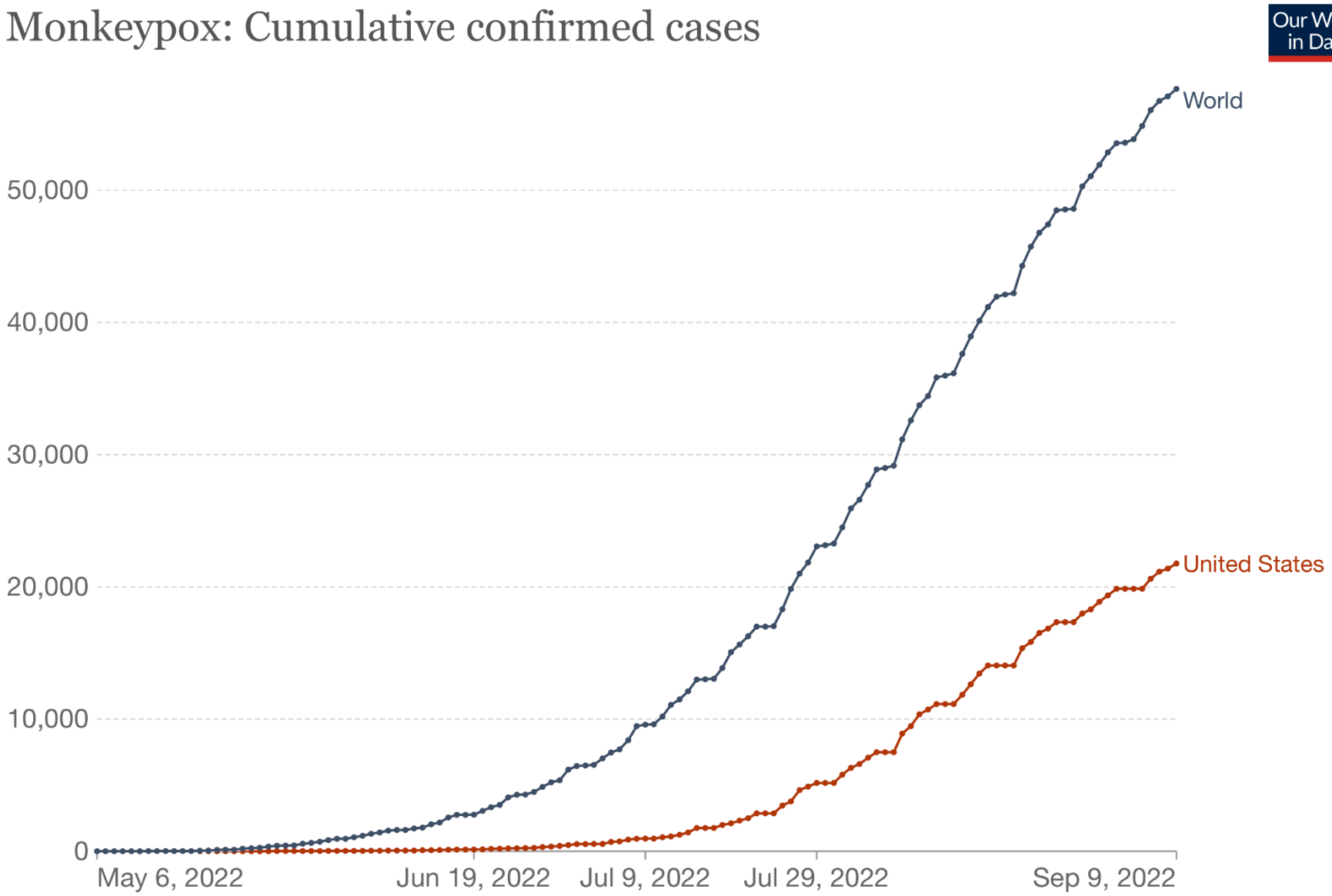
Monkeypox: Cumulative confirmed cases



Source: Data produced by the 'Global.health' team — available at github.com/globaldothealth/monkeypox

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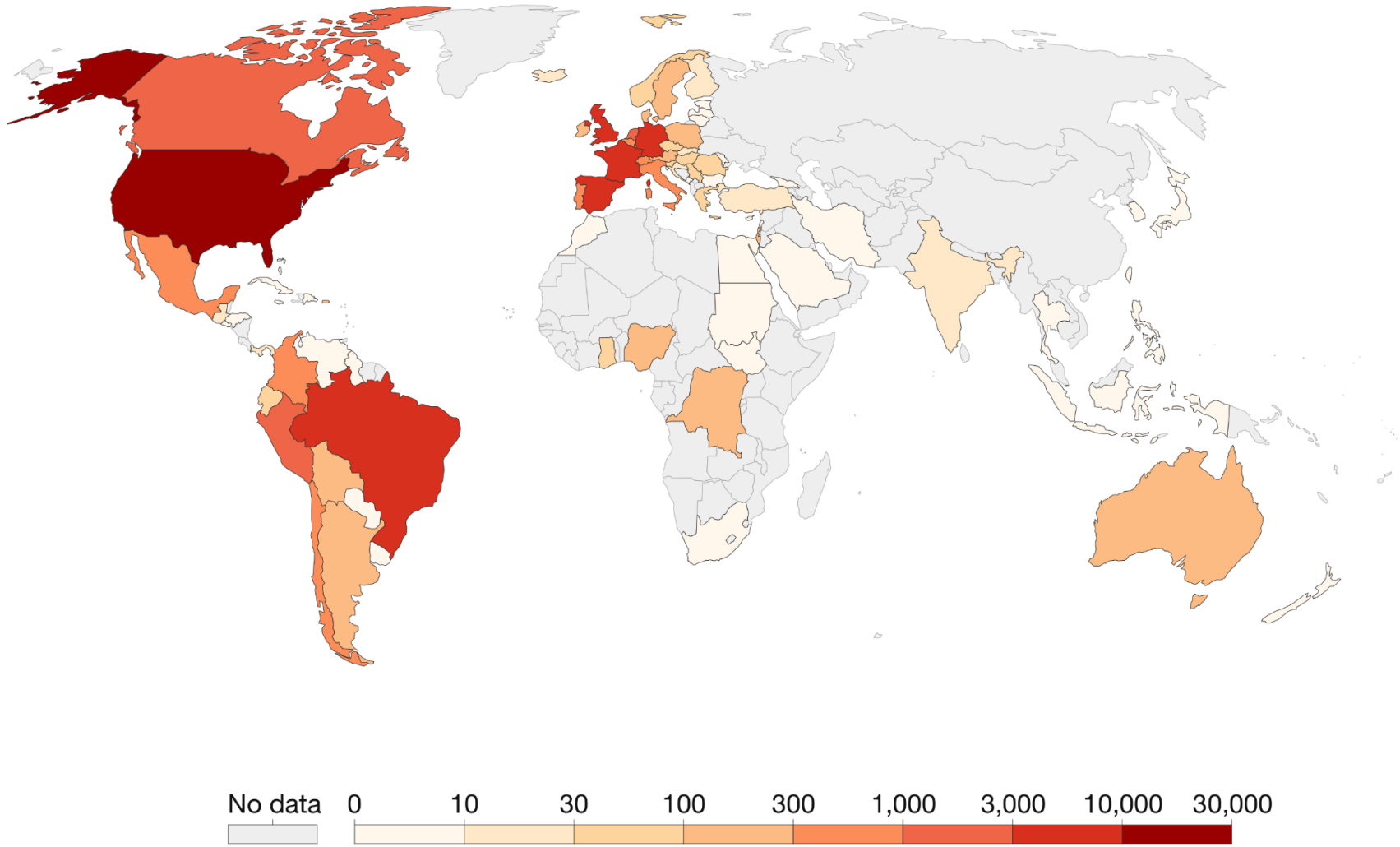
Monkeypox: Cumulative confirmed cases, Sep 9, 2022

Our World in Data



Source: Data produced by the 'Global.health' team — available at github.com/globaldothealth/monkeypox

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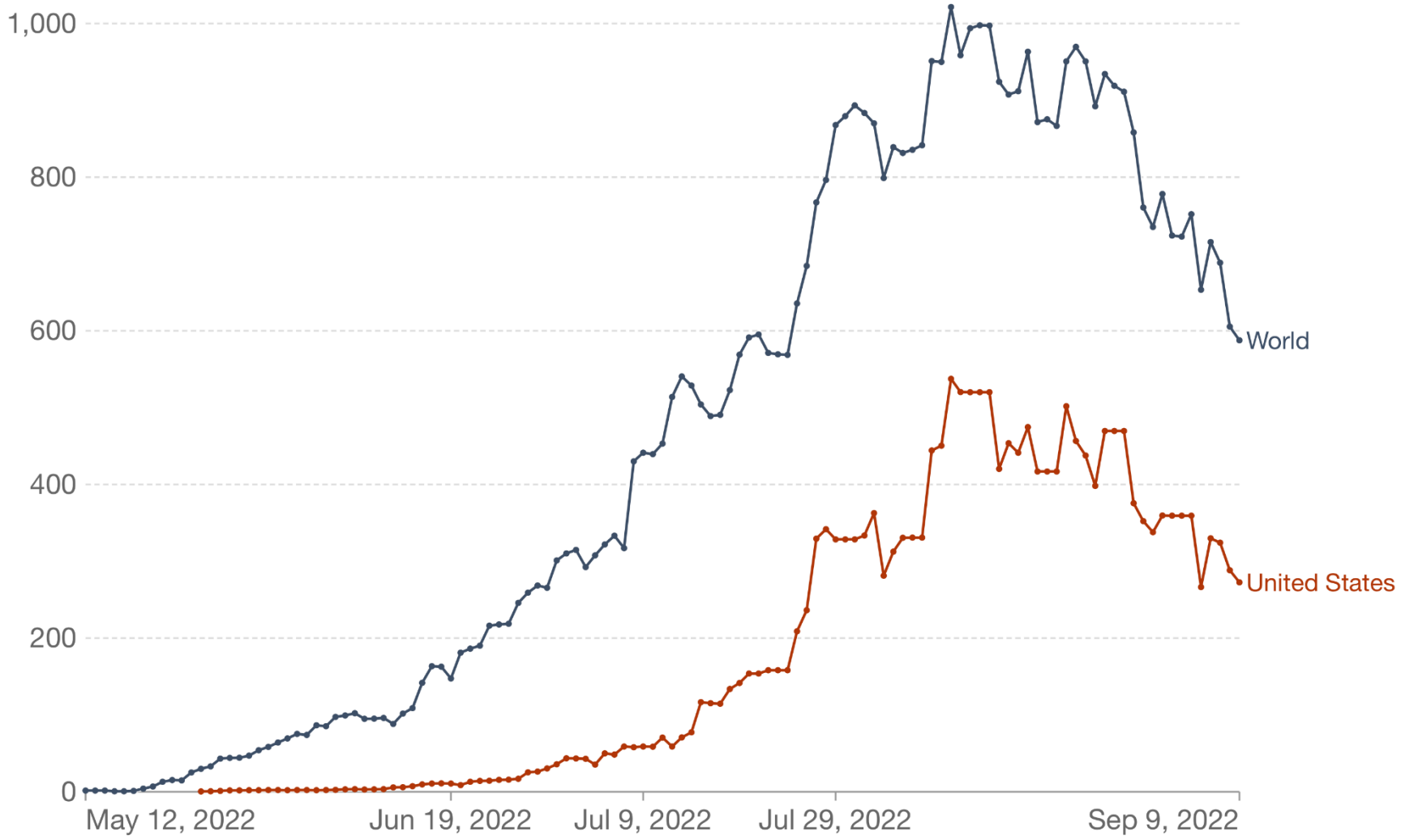
Monkeypox: Daily confirmed cases

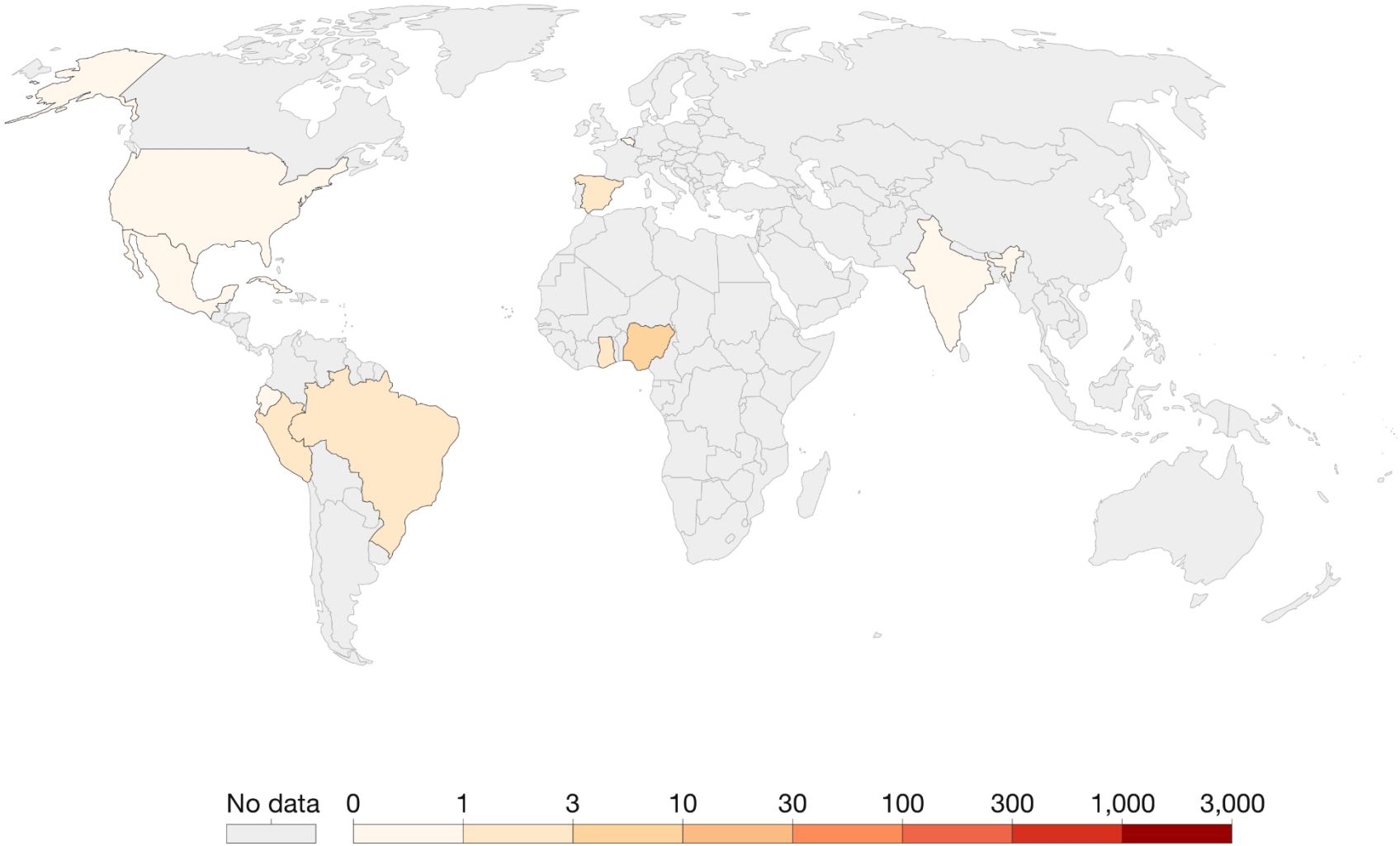
7-day rolling average



Source: Data produced by the 'Global.health' team — available at github.com/globaldothealth/monkeypox

Monkeypox: Cumulative confirmed deaths, Aug 29, 2022

Our World in Data



Source: Data produced by the 'Global.health' team — available at github.com/globaldothealth/monkeypox

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Monkeypox – Pathophysiology

- Similar to smallpox[1]; not well understood
- Primary mode of viral entry skin inoculation vs. inhalation
- Once inoculated, rapid replication within lymphatic tissue
    a) Primary viremia
    b) Dissemination to lymphoid organs (ex. spleen)
    c) Secondary viremia
    d) Localization in dermal blood vessels, infection of epidermal cells
    e) Deeper extension into dermis and sebaceous glands

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[1] *Lancet*. 2006;367(9508):425.

Monkeypox – Clinical Presentation(s)

- Historically, characteristic rash preceded by prodrome[1]
  a) Lymphadenopathy a key distinguishing factor
- **Presenting atypically with current outbreak[2]**
  a) Rash may start in genital, perianal areas ± dissemination
  b) Oral lesions
  c) Absence of prodromal symptoms
  d) Anorectal pain, tenesmus, rectal bleeding, proctitis

[1] *Clin Infect Dis.* 2014;58(2):260-7.
[2] *MMWR Morb Mortal Wkly Rep*. 2022;71(23):764.

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Monkeypox – Clinical Presentation(s)

- Incubation period: 5-13 days (4 – 21)[1,2]
- Non-specific lab abnormalities may be present
- Prodrome may last up to 5 days
- Rash typically begins 1-4 days after fever onset
    a) **Macular to papular to vesicular to pustular**
    b) Number of lesions varies
    c) Varying stages; may be confluent
    d) **May be extremely painful***

[1] *Clin Infect Dis.* 2014;58(2):260-7.
[2] *MMWR Morb Mortal Wkly Rep*. 2022;71(23):764.

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Stage	Stage Duration	Characteristics
Enanthem		▪ The first lesions to develop are on the tongue and in the mouth
Macules	1–2 days	▪ Following the enanthem, a macular rash appears on the skin, starting on the face and spreading to the arms and legs and then to the hands and feet, including the palms and soles ▪ The rash typically spreads to all parts of the body within 24 hours becoming most concentrated on the face, arms, and legs (centrifugal distribution)
Papules	1–2 days	▪ By the third day of rash, lesions have progressed from macular (flat) to papular (raised)
Vesicles	1–2 days	▪ By the fourth to fifth day, lesions have become vesicular (raised and filled with clear fluid)
Pustules	5–7 days	▪ By the sixth to seventh day, lesions have become pustular (filled with opaque fluid) – sharply raised, usually round, and firm to the touch (deep seated) ▪ Lesions will develop a depression in the center (umbilication) ▪ The pustules will remain for approximately 5 to 7 days before beginning to crust
Scabs	7–14 days	▪ By the end of the second week, pustules have crusted and scabbed over ▪ Scabs will remain for about a week before beginning to fall off

Clinical Recognition, Monkeypox. June 2022. CDC.

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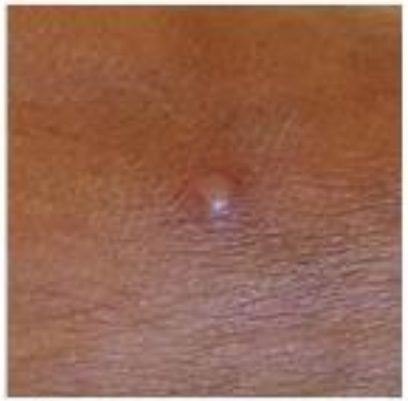
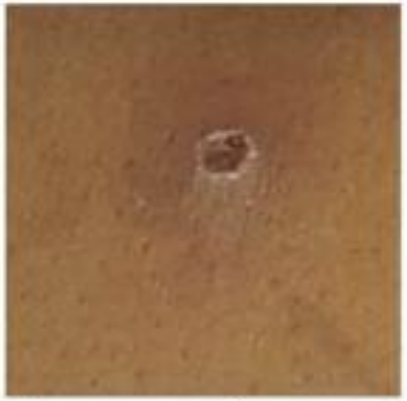


a) early vesicle, 3mm diameter

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

Image courtesy of UK Health Security Agency

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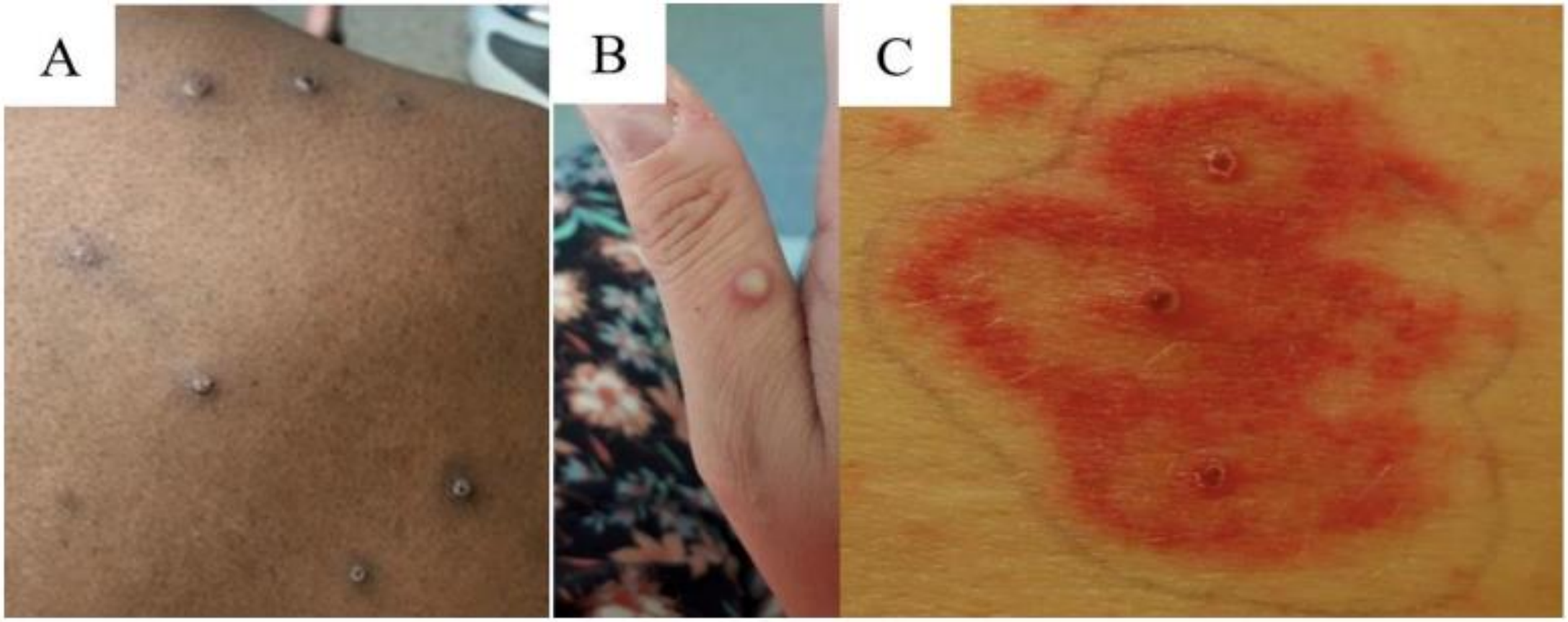

Image courtesy of CDC Clinician Outreach and Communication Activity, June 2022

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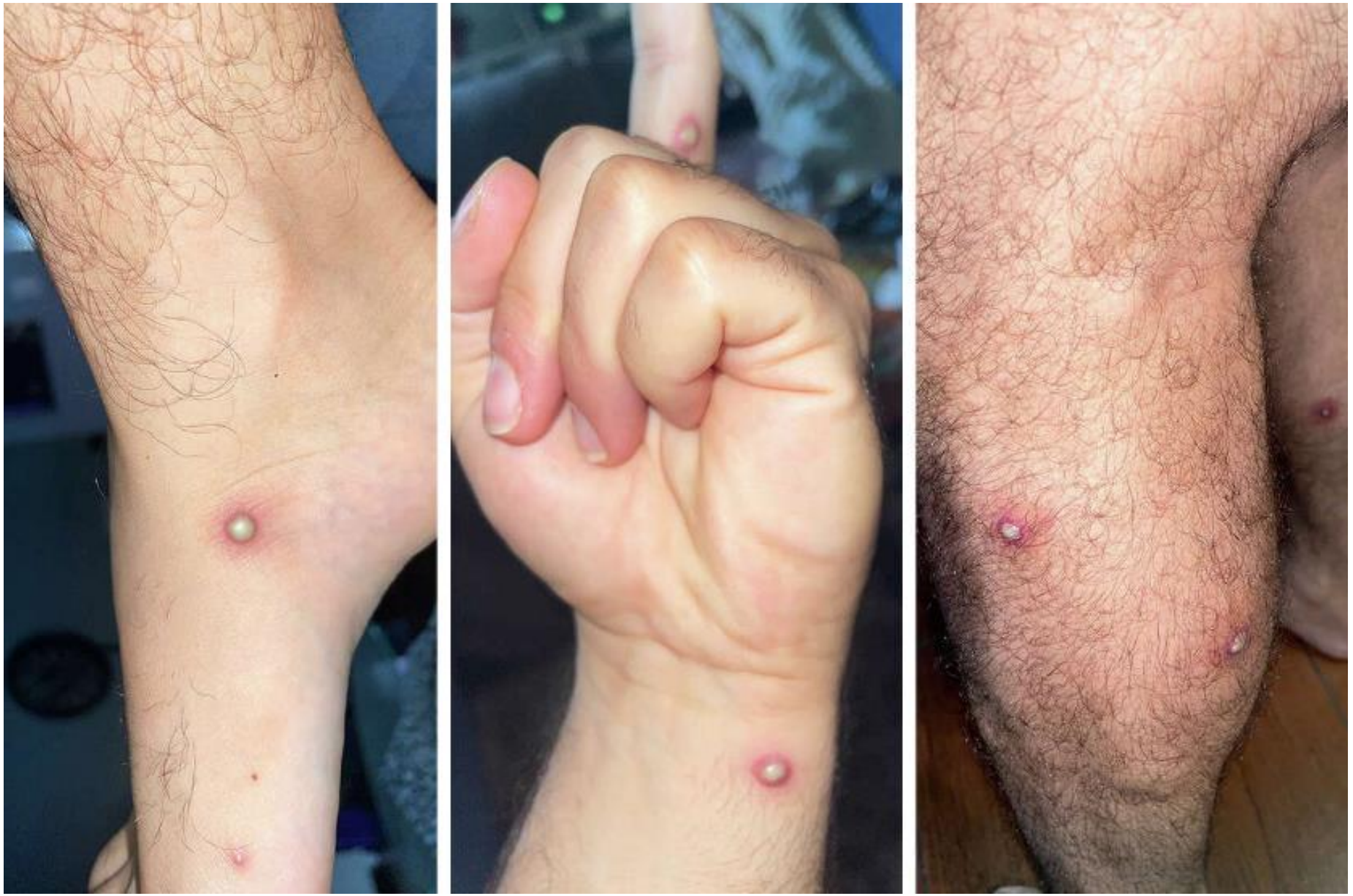

Image courtesy of The Houston Chronicle

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Monkeypox – Outcomes

- Typically self-limiting illness
- Complications:
    a) Pulmonary disease
    b) Dehydration
    c) Encephalitis
    d) Ocular infections
    e) **Pitted scarring***

[1] World Health Organization. Monkeypox fact sheet. 2022.

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Monkeypox – Diagnosis

- Should have high suspicion in the following scenarios[1,2]:
  a) Rash or other MPXV symptoms and epidemiologic risk factors
  b) Patients with genital ulcer disease and/or proctitis not responding to conventional treatment
- **Gold standard for diagnosis = (+) PCR of lesions**
  a) Minimum of 3 lesion specimens; 2 swabs per lesion
  b) ?Role of serology

[1] U.S. Centers for Disease Control and Prevention. Update for clinicians on testing and treatment for monkeypox. 2022.
[2] Monkeypox Outbreak: Updates on the Epidemiology, Testing, Treatment, and Vaccination. COCA Call. 2022.

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Monkeypox – Diagnosis

- No other circulating orthopoxviruses in the U.S. at this time
- Testing can be done either at a Laboratory Response Network (LRN) site or other commercial laboratory[1,2]
    a) LRN: perform non-variola Orthopoxvirus (NVO)-specific PCR
    b) **Samples need to be sent to CDC for MPXV-specific PCR**

[1] U.S. Centers for Disease Control and Prevention. Update for clinicians on testing and treatment for monkeypox. 2022.
[2] Monkeypox Outbreak: Updates on the Epidemiology, Testing, Treatment, and Vaccination. COCA Call. 2022.

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Monkeypox – Differential Diagnosis

- Careful assessment needed
- Consider other infectious etiologies that may mimic MPXV:
  a) **Varicella*** → ± lymphadenopathy, staging of lesions
  b) Herpes simplex virus → severity of symptoms; PCR available
  c) Sexually transmitted infections
  d) Smallpox → ± lymphadenopathy
  e) Miscellaneous poxviruses

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Tecovirimat – Overview

- Also known as TPOXX®, ST-246
  a) Inhibitor of orthopoxvirus VP37 envelope wrapping protein
  b) FDA-approved in 2018 for the treatment of smallpox
  c) Approx. 2 million doses in Strategic National Stockpile (SNS)
  d) First human use in 2007[1]
  e) Activity vs. various orthopoxviruses
  f) **NO RCTs re: efficacy in humans**
  g) Expanded access IND allows use for MPXV

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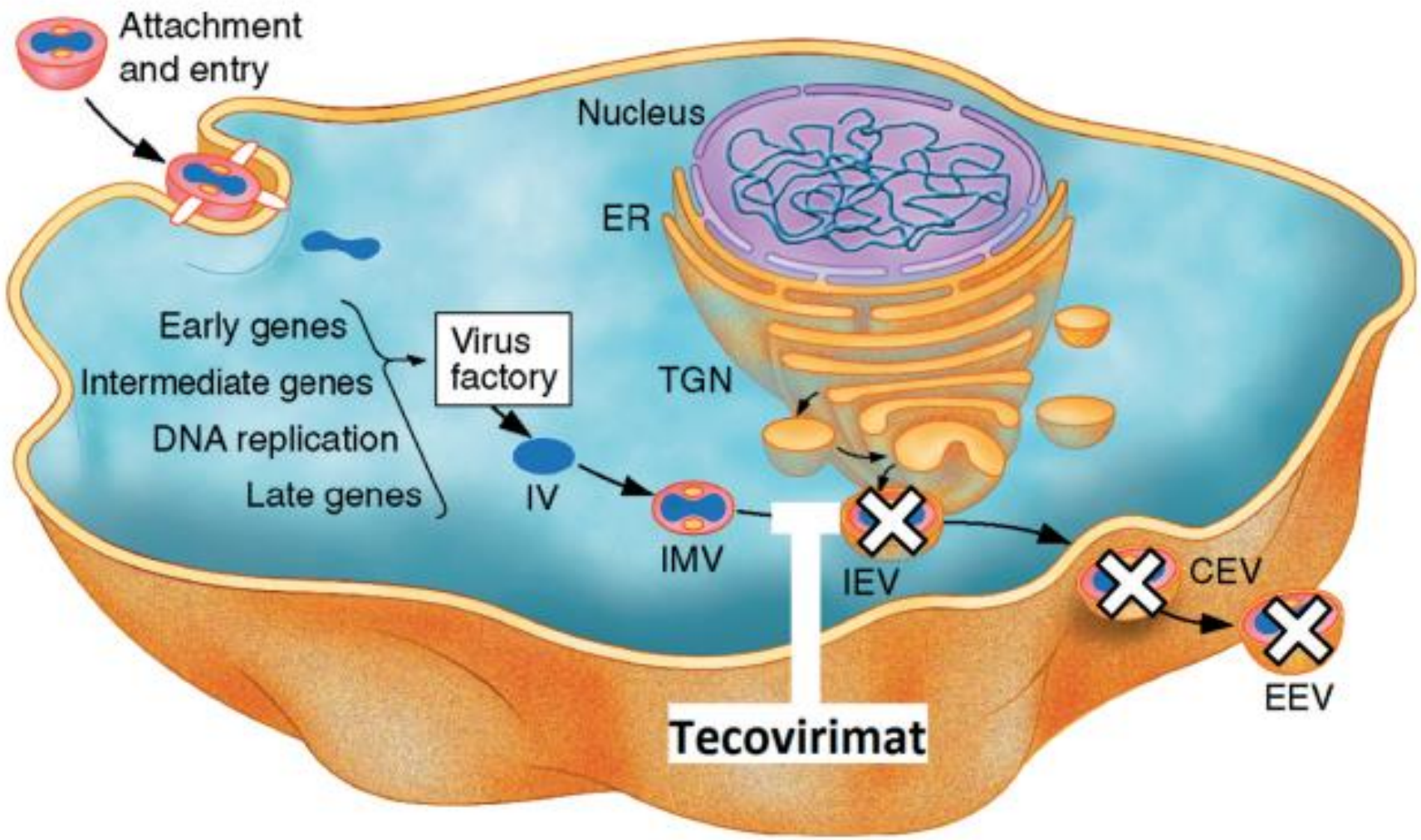
[1] *Clin Infect Dis*. 2008;46(10):1555-61.



Expert Rev Anti Infect Ther. 2021;19(3):331-44.

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Tecovirimat – Dosing (PO)

4.1 Oral Therapy for Adults and Children

Table 1. Recommended Oral Dosage Instructions for 14 Days*

Weight (kg)**	Weight (lbs)	Recommended Dose (mg)*
< 6	<13	50 mg (¼ capsule) every 12 hours
6 to < 13	13 to < 28	100 mg (½ capsule) every 12 hours
13 to < 25	28 to < 55	200 mg (1 capsule) every 12 hours
25 to < 40	55 to < 88	400 mg (2 capsules) every 12 hours
40 to < 120	88 to < 264	600 mg (3 capsules) every 12 hours
120 and above	≥ 264	600 mg (3 capsules) every 8 hours

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[1] IND 116,039 Tecovirimat (CDC IRB #6402). Version 6.0. 2022.

A	B	C	D	E
Child's weight in pounds*	**Dose**	**Number of tecovirimat capsules needed to prepare the dose**	**Amount of water or food to add**	**How much of the drug-food mixture to give your child**
Under 13 pounds	¼ capsule (50 mg)	1 	2 tablespoons (30 mL) of water	After mixing the capsule contents and water, measure out ½ tablespoon (equal to 1.5 TEAspoons or 7.5 mL) of the drug-water mixture and add to 1 tablespoon of breast milk or prepared formula in a baby bottle. Mix well. Give all the liquid in the bottle in one sitting. Give this amount 2 times each day. Throw out the unused drug-water mixture.
13 to 27 pounds	½ capsule (100 mg)	1 	2 tablespoons (30 mL) of water	After mixing the capsule contents and water, measure out 1 tablespoon (equal to 3 TEAspoons or 15 mL) of the drug-water mixture and add to 1 tablespoon of breast milk, prepared formula, or milk in a baby bottle or small bowl. Mix well. Give all the liquid to the child in one sitting via a baby bottle, an oral syringe or by spoon. Give this amount 2 times each day. Throw out the unused drug-water mixture.
28 to 54 pounds	1 capsule (200 mg)	1 	2 tablespoons (30 mL) of food or liquid	Give all of the drug-food mixture. Give this amount 2 times each day.
55 to 87 pounds	2 capsules (400 mg)	2 	2 tablespoons (30 mL) of food or liquid	Give all of the drug-food mixture. Give this amount 2 times each day.
88 to 264 pounds	3 capsules (600 mg)	3 	2 tablespoons (30 mL) of food or liquid	Give all of the drug-food mixture. Give this amount 2 times each day.
More than 264 pounds	3 capsules (600 mg)	3 	2 tablespoons (30 mL) of food or liquid	Give all of the drug-food mixture. Give this amount 3 times each day.

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Tecovirimat – Dosing (IV)

4.2 IV Therapy for Adults and Children

IV tecovirimat is contraindicated in patients with severe renal impairment (creatinine clearance <30 mL/min).

Table 2. Recommended Pediatric and Adult Tecovirimat Injection for IV Infusion[a]

Weight (kg)	Weight (lbs)	Recommended Dose	Volume of IV Tecovirimat[b]	Volume of Diluent[c]	Total Volume for Infusion
<35 kg[d]	< 77 lbs	6 mg/kg every 12 hours by IV infusion over 6 hours	0.6 mL/kg	1.2 mL/kg	Varies by weight
35 kg to <120 kg	77 to < 264 lbs	200 mg every 12 hours by IV infusion over 6 hours	20 mL	40 mL	60 mL
120 kg and above[f]	≥ 264 lbs	300 mg every 12 hours by IV infusion over 6 hours	30 mL	60 mL	90 mL

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[1] IND 116,039 Tecovirimat (CDC IRB #6402). Version 6.0. 2022.

Tecovirimat – Dose Adjustments

- PO formulation requires **no dose adjustments**
- IV formulation contains hydroxypropyl-β-cyclodextrin
  a) Contraindicated if CrCl <30 mL/min
  b) Caution if <2 years of age
  c) Risk vs. benefit

[1] IND 116,039 Tecovirimat (CDC IRB #6402). Version 6.0. 2022.

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Tecovirimat – Drug Interactions

- Substrate of UGT1A1, UGT1A4
- **Weak** inducer of CYP3A4
- **Weak** inhibitor of CYP2C9, CYP2C19

Table 3. Significant Drug Interactions

Concomitant Drug Class: Drug Name	Effect on Concentration[a]	Clinical Effect/Recommendation
Blood Glucose-Lowering Agent:		
Repaglinide[b]	↑ repaglinide	Monitor blood glucose and monitor for hypoglycemic symptoms in patients when tecovirimat is co-administered with repaglinide
Central Nervous System Depressant:		
Midazolam[b]	↓ midazolam	Monitor for effectiveness of midazolam

[a] ↓ = decrease, ↑ = increase

[b] These interactions have been studied in healthy adults.

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[1] IND 116,039 Tecovirimat (CDC IRB #6402). Version 6.0. 2022.

Tecovirimat – Safety (PO)

- *N Engl J Med*. 2018;379(1):44-53
  a) Phase 3 safety, tolerability, PK study in healthy individuals
  b) TPOXX® 600 mg PO q12H (N=359) vs. placebo (N=90) x14 days
  c) **59% female**
  d) **69% Caucasian**, 28% Black/African American, 12% Hispanic or Latino, 1% Asian
  e) 10% (N=36) greater than 65 years of age
     i. 1% (N=4) >75

Tecovirimat – Safety (PO)

- *N Engl J Med*. 2018;379(1):44-53

Table 3: Treatment-Related Adverse Reactions Reported in ≥ 2% of Healthy Adult Subjects Receiving at Least One Dose of TPOXX Capsules 600 mg

Adverse Reaction	TPOXX 600 mg N = 359 (%)	Placebo N = 90 (%)
Headache	12	8
Nausea	5	4
Abdominal pain[a]	2	1
Vomiting	2	0

[a]Includes abdominal pain, abdominal pain upper, abdominal distension, abdominal discomfort, abdominal pain lower, epigastric pain

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Tecovirimat – Safety (IV)

- Tecovirimat [package insert]. Corvallis, OR: SIGA Technologies, 2022
  a) TPOXX® 240 mg IV q12H (N=26) vs. placebo (N=6) x7 days
  b) **58% male**
  c) **69% Caucasian**, 42% Hispanic or Latino, 23% Black/African American

Table 4: Treatment-Related Adverse Reactions Reported in ≥ 4% of Healthy Adult Subjects Receiving at Least One Dose of TPOXX Injection 240 mg

	TPOXX 240 mg N =26 (%)	Placebo N = 6 (%)
Infusion Site Pain	73	67
Infusion Site Swelling	39	67
Infusion Site Erythema	23	67
Infusion Site Extravasation	19	50
Headache	15	0

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Tecovirimat – Pharmacokinetics

Table 6: Pharmacokinetic Properties of Tecovirimat

Absorption	**200 mg intravenous**	**600 mg oral**
Median T_{max} (h) (Range)	6 (6-6.5)	6 (2-24)[a]
Effect of food (relative to fasting)	NA	↑39% [b]
Distribution		
% Bound to human plasma proteins	77-82	
Blood-to-plasma ratio (drug or drug-related materials)	0.62-0.90	
Volume of distribution (Vz or Vz/F, L) (CV%)	383 (46%)	1030
Metabolism		
Metabolic pathways[c]	Hydrolysis, UGT1A1[d], UGT1A4	
Elimination		
Major route of elimination	Metabolism	
Clearance (CL or CL/F, L/hr) (CV%)	13 (23%)	31
$t_{½}$ (h)[e] (CV%)	21 (45%)	19(29%)
% of dose excreted in urine[f]	NA	73, predominantly as metabolites
% of dose excreted in feces[f]	NA	23, predominantly as tecovirimat

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[1] IND 116,039 Tecovirimat (CDC IRB #6402). Version 6.0. 2022.

Tecovirimat – Special Populations

- Pregnancy and lactation
  a) No human data
  b) Animal studies did not demonstrate development of embryo-fetal abnormalities
  c) Detected in milk of lactating mice
  d) **Breastfeeding not recommended if active lesions**
- Females and males of reproductive age
  a) No human data
  b) Decreased fertility due to testicular toxicity seen in mice

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[1] IND 116,039 Tecovirimat (CDC IRB #6402). Version 6.0. 2022.

Tecovirimat – Special Populations

- Pediatrics
    a) No human data
- Geriatrics
    a) Limited safety data

[1] IND 116,039 Tecovirimat (CDC IRB #6402). Version 6.0. 2022.

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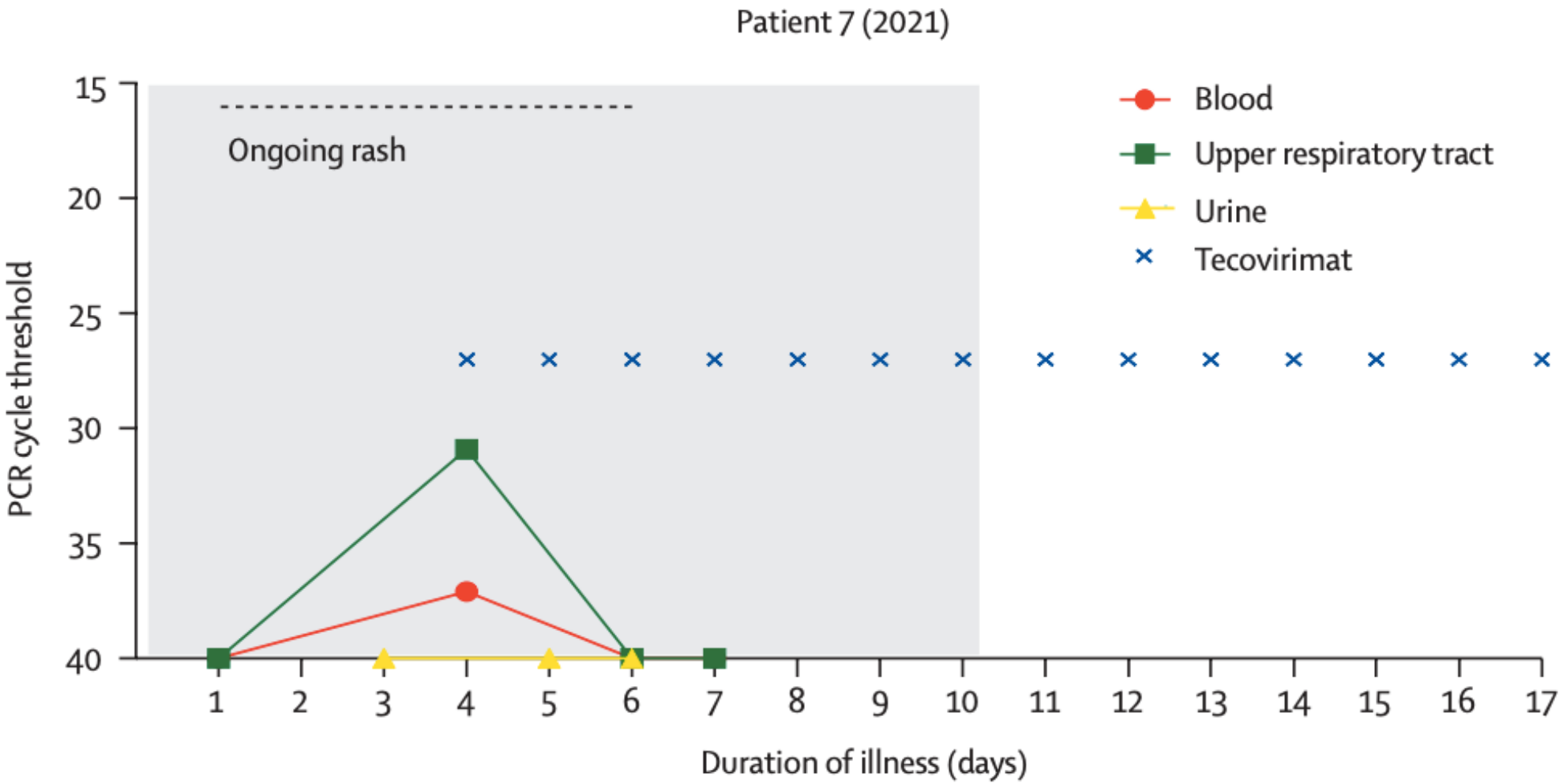
Tecovirimat – Case Reports (Pre-2022)

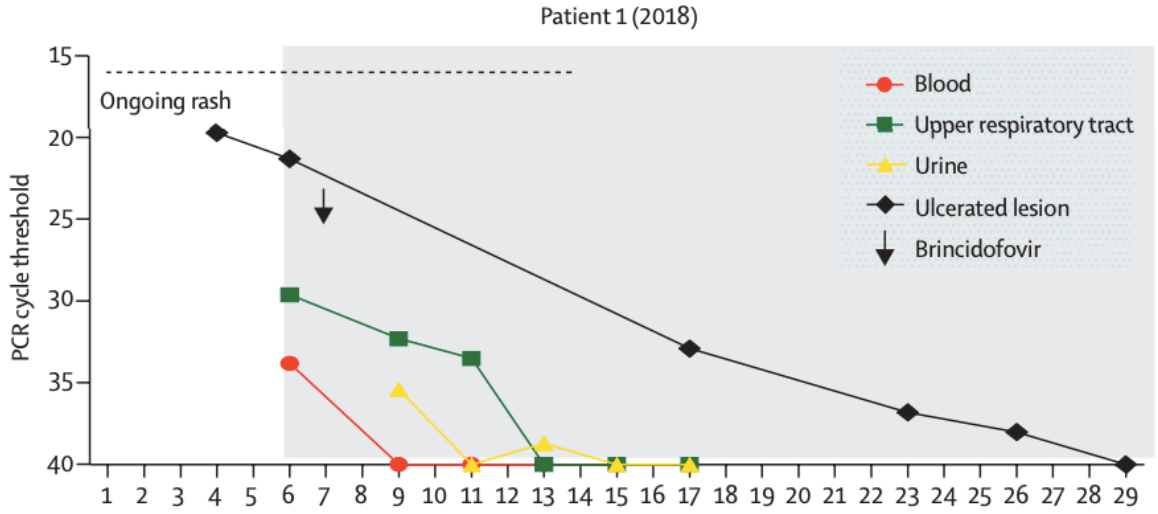
- *MMWR Morb Mortal Wkly Rep*. 2022;71(14):509
  a) July 2021 – middle-aged male presents to Dallas hospital ED with fever, cough, fatigue, nausea, vomiting, extensive pustular rash on face
  b) Recent travel to Nigeria
  c) LRN confirmed presence non-variola orthopoxvirus
  d) **MPXV confirmed by CDC**
  e) Started on TPOXX® 600 mg PO q12H x19 doses, transitioned to IV
  f) Resolution of symptoms, no treatment-associated ADRs

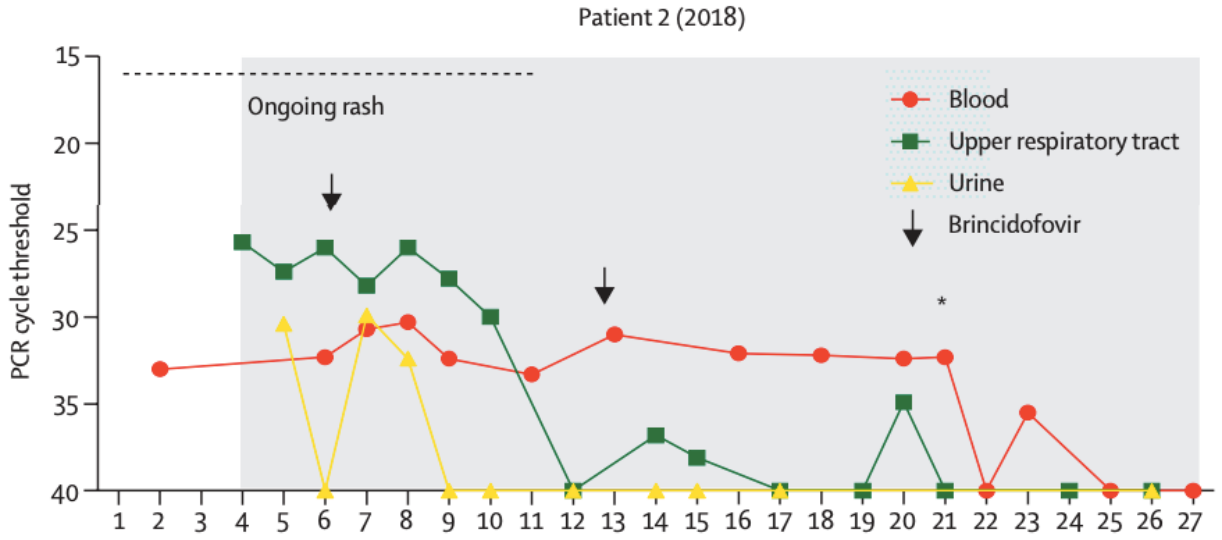
Tecovirimat – Case Reports (Pre-2022)

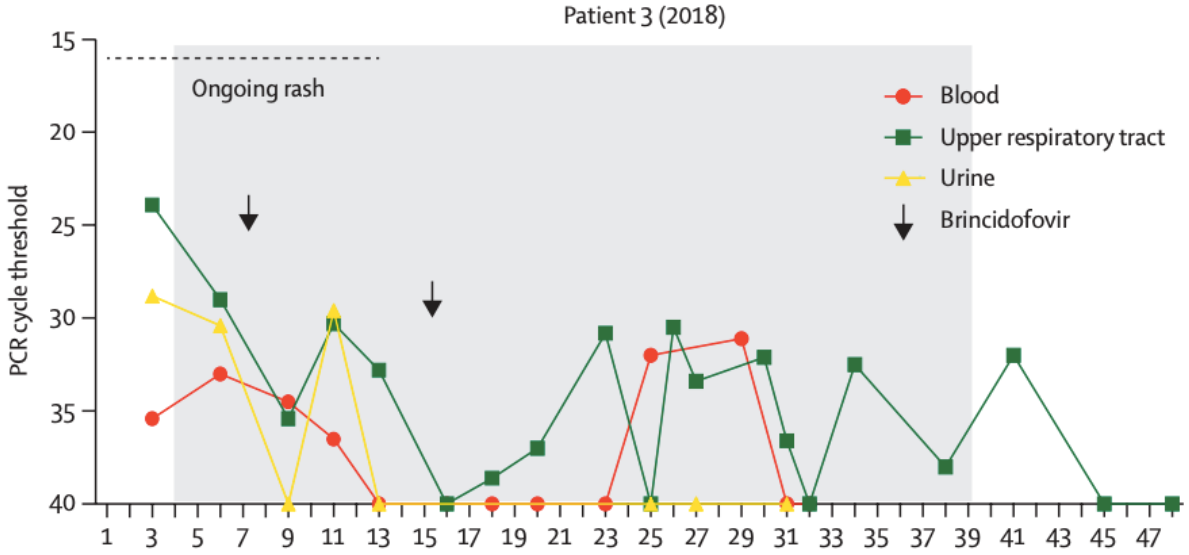
- *Lancet Infect Dis*. 2022;22(8):1153-62
  a) 3 patients received brincidofovir; **1 received TPOXX®**
  b) 30 to 40-year-old female from Liverpool
  c) 10 lesions
  d) Viral DNA detected in blood, nose, throat
  e) Started on TPOXX® 600 mg PO q12H on D5 of illness
  f) Discharged on hospital D10, full recovery



Lancet Infect Dis. 2022;22(8):1153-62.







Lancet Infect Dis. 2022;22(8):1153-62.

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Tecovirimat – Case Reports

- *Open Forum Infect Dis*. 2022;9(8):ofac377
  a) Case 1 – man in his 20's
     i. Chills, malaise, shallow ulcer on foreskin → vesiculopustular lesions on face, oropharynx, hands, feet, pubis
     ii. TPOXX® 600 mg PO q12H started on D2
     iii. **New lesions had ceased by D4 of therapy**
     iv. Mild LFTs abnormalities noted on D6 of therapy
     v. Completed 14 days of treatment w/**reported resolution of majority of lesions**

Tecovirimat – Case Reports

- *Open Forum Infect Dis*. 2022;9(8):ofac377
  a) Case 2 – man in his 20's w/HIV
     i. Presented after anal-receptive intercourse with a confirmed MPXV case
     ii. PEP w/Jynneos® → **fever, chills, myalgias, tonsillar pain, odynophagia, erythematous pustules on forearms, hands**
     iii. TPOXX® 600 mg PO q12H started on D2
     iv. Developed additional pustular lesions on gingiva, upper, lower extremities
     v. Completed 14 days of treatment w/**crusting of all lesions by D9**

Tecovirimat – Case Reports

- *Open Forum Infect Dis*. 2022;9(8):ofac377
  a) Case 3 – man in his 40's on PrEP
    i. Malaise, fevers, maculopapular rash of the perineum → **confluent erythematous rash of the perineum w/umbilicated pustules on the foreskin, chest, arms, R-lower eyelid**
    ii. TPOXX® 600 mg PO q12H started on D2
    iii. Improvement in perineal rash, resolution of pustular lesions by D2 of treatment
    iv. Completed 14 days of treatment w/**near-complete resolution of symptoms by D7**

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Tecovirimat – Treatment Considerations

- Under E-IND:
  a) Primary or early empiric treatment
     i. Confirmed non-variola orthopoxvirus infection
     ii. **Suspected infection***
  b) Secondary treatment
     i. ± vaccinia immune globulin
  c) Post-exposure prophylaxis

[1] IND 116,039 Tecovirimat (CDC IRB #6402). Version 6.0. 2022.

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Treatment Consideration

Tecovirimat may be considered for treatment in people infected with *Monkeypox virus*:

- With severe disease (e.g., hemorrhagic disease, confluent lesions, sepsis, encephalitis, or other conditions requiring hospitalization)
- Who are at high risk of severe disease:
  - People with immunocompromising conditions (e.g., HIV/AIDS, leukemia, lymphoma, generalized malignancy, solid organ transplantation, therapy with alkylating agents, antimetabolites, radiation, tumor necrosis factor inhibitors, high-dose corticosteroids, being a recipient with hematopoietic stem cell transplant <24 months post-transplant or ≥24 months but with graft-versus-host disease or disease relapse, or having autoimmune disease with immunodeficiency as a clinical component)
  - Pediatric populations, particularly patients younger than 8 years of age
  - Pregnant or breastfeeding women
  - People with a history or presence of atopic dermatitis, people with other active exfoliative skin conditions (e.g., eczema, burns, impetigo, varicella zoster virus infection, herpes simplex virus infection, severe acne, severe diaper dermatitis with extensive areas of denuded skin, psoriasis, or Darier disease [keratosis follicularis])
  - People with one or more complication (e.g., secondary bacterial skin infection; gastroenteritis with severe nausea/vomiting, diarrhea, or dehydration; bronchopneumonia; concurrent disease or other comorbidities)
- With aberrant infections involving accidental implantation in eyes, mouth, or other anatomic areas where *Monkeypox virus* infection might constitute a special hazard (e.g., the genitals or anus)

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Tecovirimat – Treatment Considerations

- Consider IV if:
  a) Swallowing difficulties
  b) Concern for impaired PO drug absorption
     i. Critically ill patients
     ii. GI disfunction, gastric bypass

[1] IND 116,039 Tecovirimat (CDC IRB #6402). Version 6.0. 2022.

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Tecovirimat – How to Obtain

- Available via SNS in collaboration with state/local health departments
  a) After hours: CDC Emergency Operations Center (770-488-7100)
- **Can begin after obtaining informed consent**

Required

1. **Informed Consent Form** English [268 KB, 6 pages] | Spanish [335 KB, 6 pages]: Obtain prior to treatment.
   - Alternative Short Form Consent [134 KB, 3 pages] and Written Summary [230 KB, 5 pages] that can be used to obtain informed consent
2. Patient Intake Form [338 KB, 2 pages]: Baseline assessment.
3. FDA Form 1572 [1 MB, 2 pages]: One signed 1572 per facility suffices for all TPOXX treatments administered under the EA-IND at the same facility.
4. **Serious Adverse Events:** Per FDA requirement, report life-threatening or serious adverse events associated with TPOXX by completing a PDF MedWatch Form [956 KB, 5 pages] and returning it to CDC via email (regaffairs@cdc.gov) or uploading to ShareFile within 72 hours of awareness or sooner, if possible. The PDF MedWatch Form can also be downloaded from the FDA website. (Note: The MedWatch Form can only be viewed on the Adobe desktop app. Please save or download the form for viewing.)

[1] IND 116,039 Tecovirimat (CDC IRB #6402). Version 6.0. 2022.

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Cidofovir

- FDA-approved for treatment of CMV retinitis in patients with AIDS
- In vitro activity against MPXV[1,2]
- Effective in MPXV challenge in animal models[3]
- **No clinical data regarding efficacy against MPXV in humans**
- **Boxed warning for nephrotoxicity**

[1] *Antiviral Res.* 2003;57(1-2):13.
[2] *Antivir Chem Chemother*. 2008;19(3):115.
[3] *Nature*. 2006;439(7077):745.

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Brincidofovir

- FDA-approved for treatment of smallpox
- Oral analog of cidofovir
- Extremely limited availability
- In vitro activity against orthopoxvirus infection[1,2,3]
- **?Efficacy in humans**[4]

[1] *mSphere.* 2021;6(1):e00927-20.
[2] *Viruses*. 2011;3(1):47.
[3] *Antiviral Res*. 2012;94(1):44.
[4] *Lancet Infect Dis*. 2022;22(8):1153-62.

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Trifluridine

- FDA-approved for herpes keratoconjunctivitis, keratitis
- Can be considered for ocular infections[1,2]
    a) Hasten recovery, prevent long-term damage[3]
- 1 drop q4H x7-10 days

[1] *Arch Ophthalmol.* 2003;121(50:715.
[2] *Viruses*. 2017; 9(12):380.
[3] *Int J Infect Dis*. 2014;21):276-7.

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Supportive Care

- Pruritus
  a) PO antihistamines
  b) Calamine lotion, hydrocortisone 2.5%
- Retinal lesions
  a) Lubricant eye drops
  b) Prophylactic antibiotic drops
- Oral lesions
  a) Viscous lidocaine 2%

Supportive Care

- Proctitis
  a) Stool softeners
  b) Sitz bath
  c) Lidocaine 4% cream
- Pain
  a) May require multimodel management
- Bacterial superinfection
  a) No role for prophylactic antibiotics
  b) Consider antibiotics for superimposed for cellulitis, abscess

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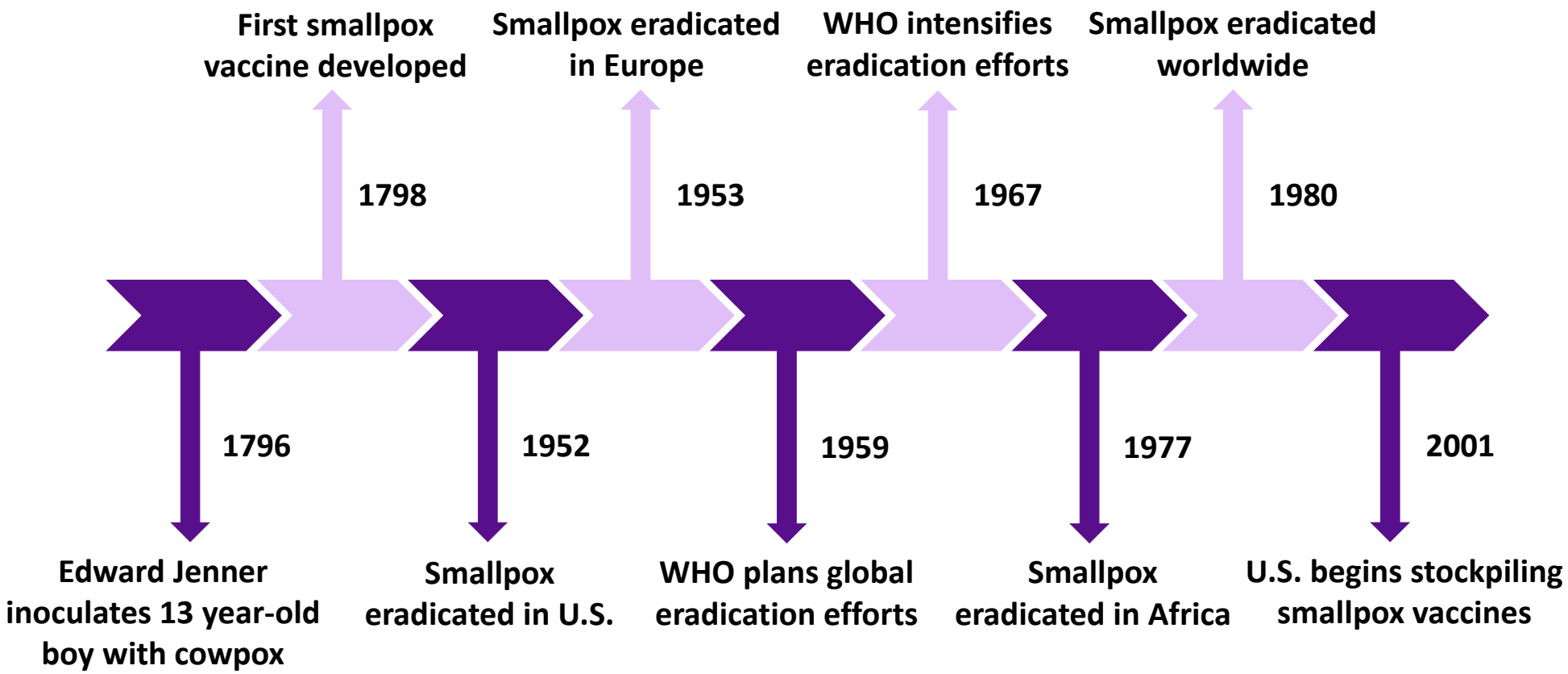
Vaccinations – Smallpox



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Vaccinations – Smallpox

- Utilizes the vaccinia virus[1]
- ?Protection vs. MPXV, other orthopoxviruses
    a) 5-fold lower risk amongst unvaccinated: 0.78 vs. 4.05 per 10,000[1]
- Two types:
    a) Vaccinia virus (**replication-competent**) vaccine
        i. Dryvax® → ACAM2000®
    b) Modified vaccinia Ankara (MVA) (**non-replicating**) vaccine
        i. Jynneos®

[1] *Mol Biol Cell*. 2001;12(7):2031-46.
[2] *Proc Natl Acad Sci USA*. 2010;107(37):16262.

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Vaccinations – ACAM2000®

- **Single-dose**, 2nd generation, replication-competent vaccine
  a) **Avoided in immunocompromised patients**
- FDA-approved for immunization against smallpox*
  a) E-IND allows for use against Non-Variola Orthopoxvirus Infection
- ?Efficacy vs. MPXV:
  a) 85% effective **vs. zoonotic MPXV infection**[1]
  b) Limited data on immunogenicity[2]
  c) No immune correlate of protection

[1] *Bulletin of the World Health Organization*. 1988;66(4):465-70.
[2] *MMWR Morb Mortal Wkly Rep*. 2016;65:257-62.

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Vaccinations – ACAM2000®

- Peak immunity reached **4 weeks** after vaccination[1]
  a) ?Duration of protection
  b) Revaccinate every 3 years
- Significant ADRs – **boxed warning**:
  a) Myocarditis/pericarditis: 5.7 per 1000 primary vaccines (95% CI 1.9-13.3)[2]
  b) Encephalitis
  c) Progressive vaccinia
  d) Eczema vaccinatum

[1] *MMWR Morb Mortal Wkly Rep*. 2016;65:257-62.
[2] *JAMA*. 2005;294(21):2734.

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Contraindications for Use of ACAM2000 Vaccine

Medical condition or history	Interim Guidance	Suggested action(s)
History of a severe allergic reaction (e.g., anaphylaxis) after a previous dose of ACAM2000	Contraindication	Do not administer. Referral to an allergist-immunologist should be considered to assess the risks versus benefits of administering a dose.
History of a severe allergic reaction (e.g., anaphylaxis) to a component of ACAM2000	Contraindication	Do not administer. Referral to an allergist-immunologist should be considered to assess the risks versus benefits of administering a dose.
Three or more major cardiac risk factors (hypertension, diabetes, hypercholesterolemia, heart disease at age <50 years in a first-degree relative, or smoking)	Contraindication	Do not administer.
Eye disease treated with topical steroids	Contraindication	Do not administer.
Congenital or acquired immune deficiency disorders, including those taking immunosuppressive medications and people living with HIV (regardless of immune status)	Contraindication	Do not administer.
Atopic dermatitis/eczema and people with a history of atopic dermatitis/eczema or other acute or exfoliative skin conditions	Contraindication	Do not administer.
Infants age <12 months	Contraindication	Do not administer.
Pregnancy or breastfeeding	Contraindication	Do not administer.
Children and adolescents ages 1 through 16 years	Precaution	Assess risks versus benefits of administering a dose; safety and effectiveness of ACAM2000 have not been established in people under age 16 years.
Moderate or severe acute illness, with or without fever	Precaution	Consider deferring vaccination until the acute illness has improved.

Adapted from CDC ACAM2000 Vaccine

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Vaccinations – ACAM2000®

- Complicated administration – 0.0025 mL droplet via percutaneous route
  a) Two-pronged aka bifurcated needle
  b) 15 repetitive pricks in a circular motion, should draw blood
  c) **Need to observe for vaccine take**
     i. Papule → vesicle → pustule
     ii. Ultimately, scab develops
  d) **Transmissible*****

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[1] ACAM2000 [package insert]. Gaithersburg, MD: Emergent Biosolutions, 2018.

Figure 1: Progression of major cutaneous reaction after primary vaccination[1]

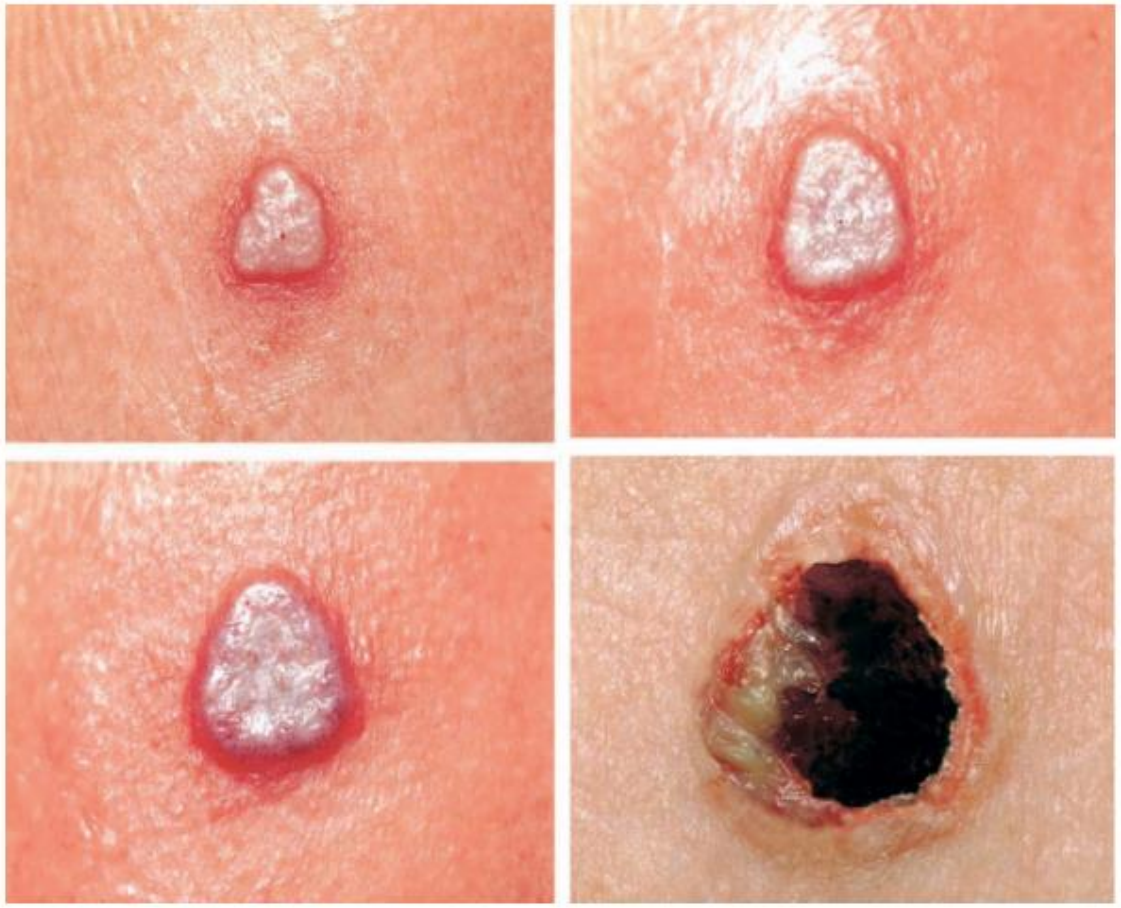
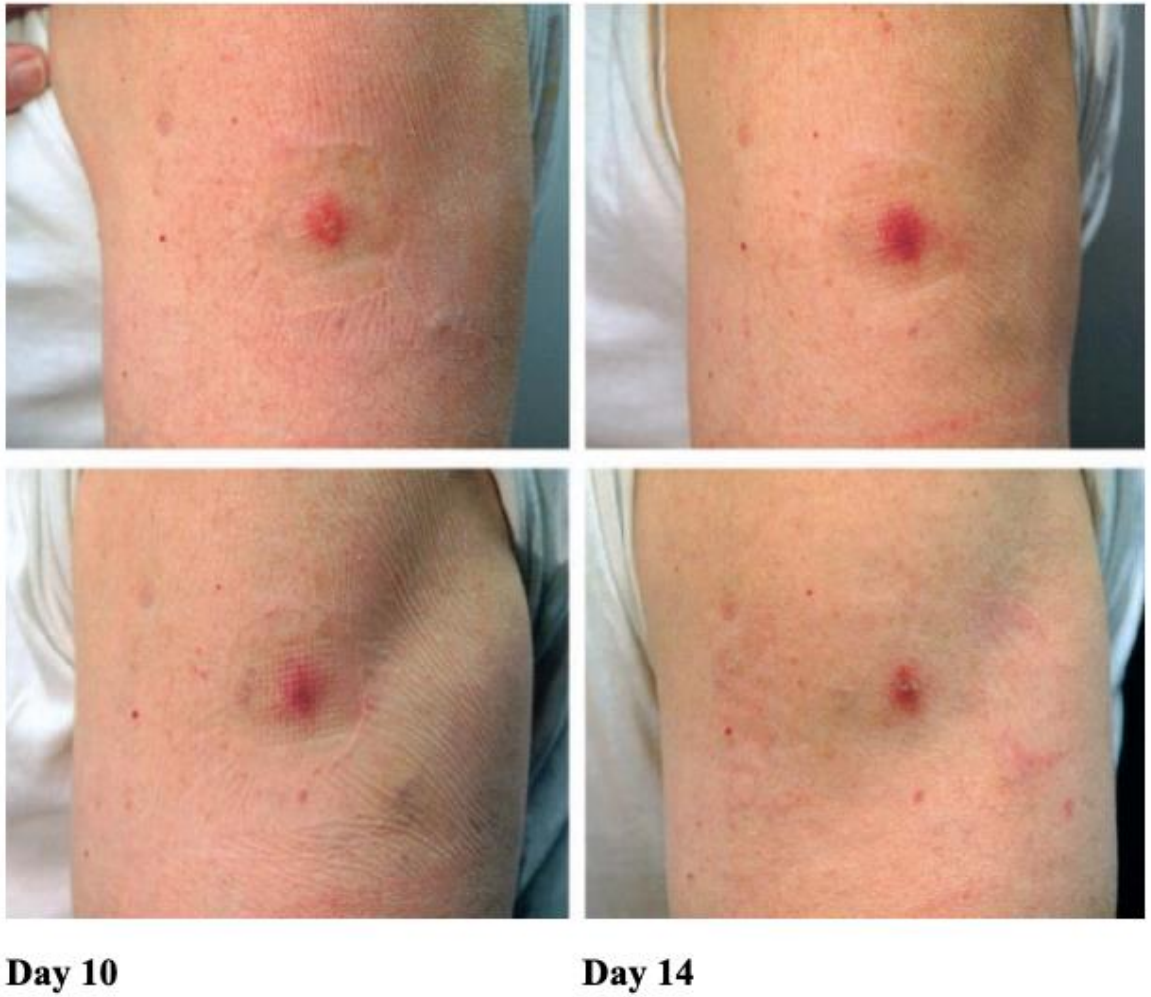


Figure 2: Progression of major cutaneous reaction after revaccination[1]



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ACAM2000 [package insert]. Gaithersburg, MD: Emergent Biosolutions, 2018.

Vaccinations – Jynneos®

- **Two dose**, 3rd generation, replication-deficient vaccine
- FDA-approved for immunization against smallpox, MPXV*
    a) E-IND allows for use in those <18 years
- ?Efficacy vs. MPXV:
    a) Comparable immune response to ACAM2000®[1]
    b) No immune correlate of protection

[1] *MMWR Morb Mortal Wkly Rep*. 2022;71:734-42.

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Vaccinations – Jynneos®

- Peak immunity reached **2 weeks** after second dose[1]
  a) ?Duration of protection
- Enhanced safety profile vs. ACAM2000®
  a) Headache, myalgias, lymphadenopathy, injection site reactions
  b) **Safe(r) option for immunocompromised patients**

[1] Jynneos [package insert]. Denmark: Bavarian Nordic A/S, 2021.

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Contraindications for Use of Jynneos Vaccine

Medical condition or history	Interim Guidance	Suggested action(s)
History of a severe allergic reaction (e.g., anaphylaxis) after a previous dose of JYNNEOS	Contraindication	Do not administer. Referral to an allergist-immunologist should be considered to assess the risks versus benefits of administering a dose.
History of a severe allergic reaction (e.g., anaphylaxis) following exposure to gentamicin or ciprofloxacin	Precaution	Discuss risks and benefits with potential recipients. They may be vaccinated with a 30-minute observation period. Alternatively, vaccination can be delayed until an allergist-immunologist is consulted, but the impact of delaying vaccination should be considered.
History of a severe allergic reaction (e.g., anaphylaxis) to chicken or egg protein AND are currently avoiding exposure to all chicken or egg products	Precaution	Discuss risks and benefits with potential recipients. They may be vaccinated with a 30-minute observation period. Alternatively, vaccination can be delayed until an allergist-immunologist is consulted, but the impact of delaying vaccination should be considered.
Moderate or severe acute illness, with or without fever	Precaution	Consider deferring vaccination until the acute illness has improved.

Adapted from CDC Jynneos Vaccine

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Table 2. Vaccination Schedule and Dosing Regimens for JYNNEOS Vaccine

JYNNEOS vaccine regimen	Route of administration	Injection volume	Recommended number of doses	Recommended interval between 1st and 2nd dose
Alternative regimen				
People age ≥18 years	ID	0.1 mL	2	28 days
Standard regimen				
People age <18 years	Subcut	0.5 mL	2	28 days
People of any age who have a history of developing keloid scars	Subcut	0.5 mL	2	28 days

Adapted from CDC Jynneos Vaccine

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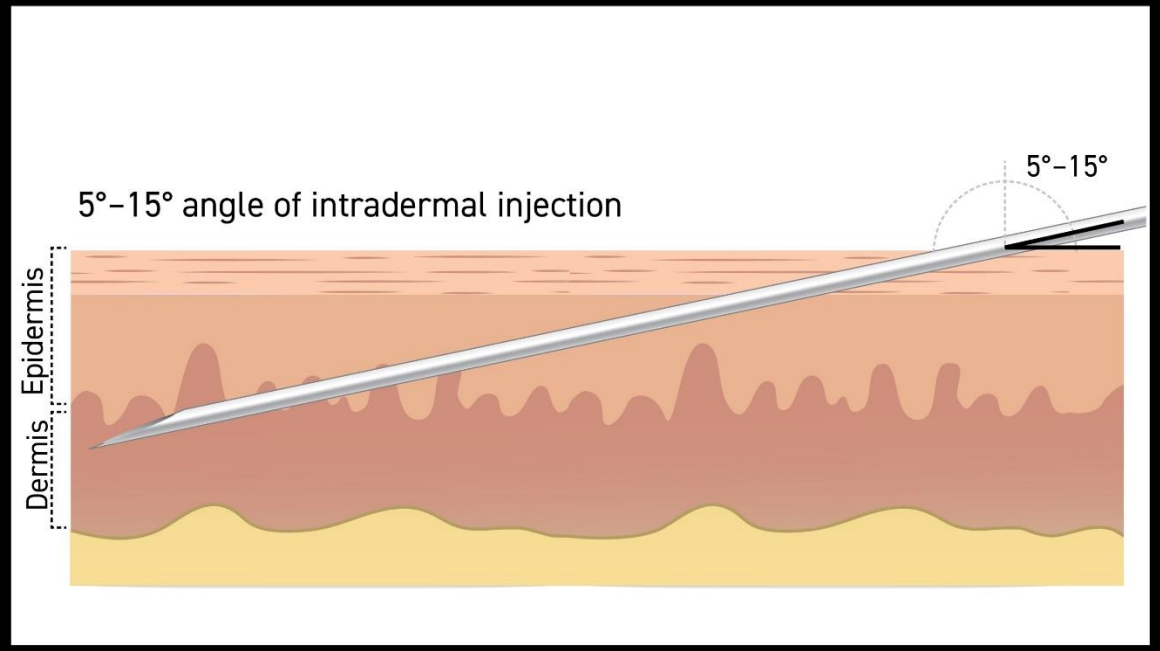
MONKEYPOX

How to administer a JYNNEOS vaccine intradermally



STEP 2

While pulling the skin taut, position the needle with the bevel facing up and insert the needle at a 5- to 15-degree angle into the dermis.

www.cdc.gov/monkeypox

CS 333451 08/09/2022

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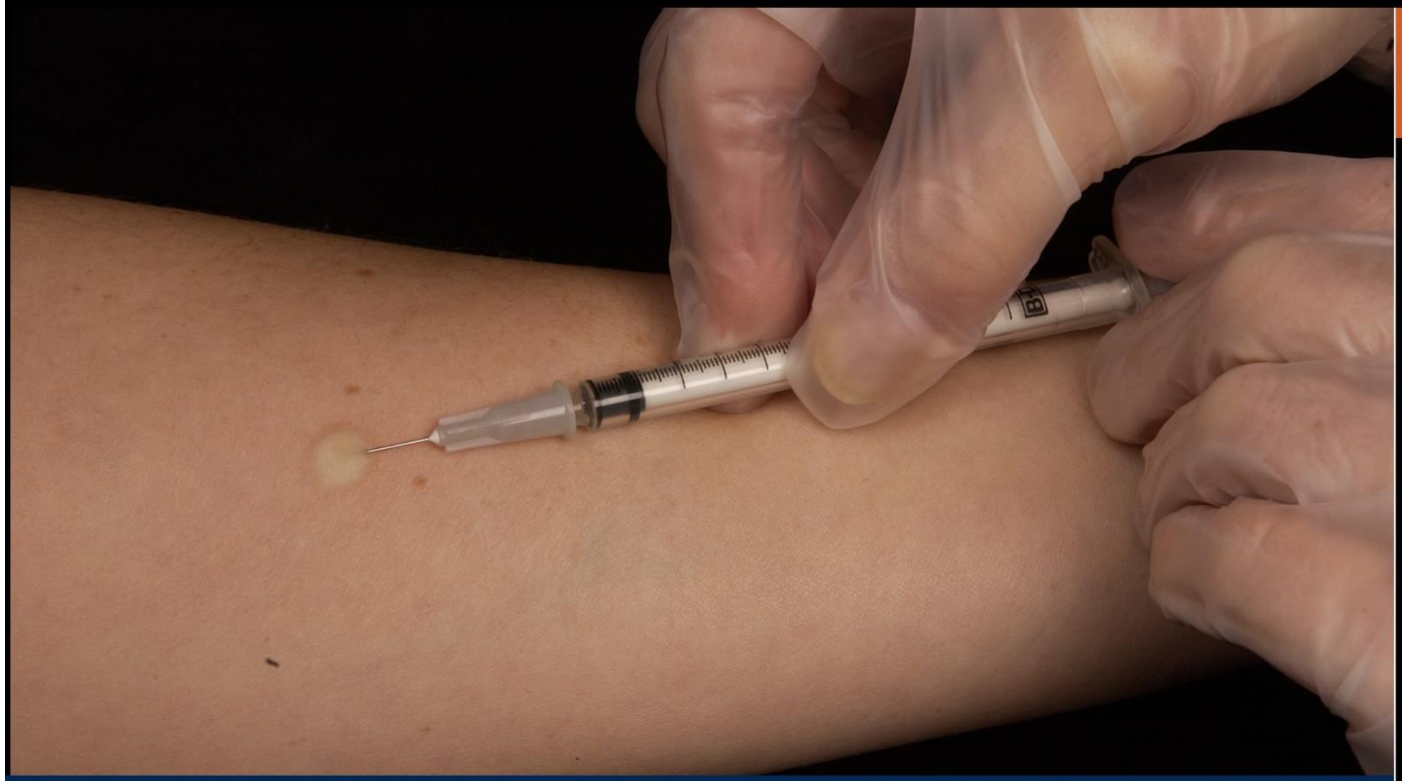
MONKEYPOX

How to administer a JYNNEOS vaccine intradermally



www.cdc.gov/monkeypox

STEP 3

Slowly inject 0.1mL intradermally.
This should produce a noticeable pale elevation of the skin (wheal).

CS 333451 08/09/2022

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Vaccinations – Special Considerations

- COVID-19 vaccines:
  a) If COVID-19 vaccine administered first: do not delay MPXV vaccination
     i. No minimum interval
  b) If MPXV vaccine administered first: consider waiting 4 weeks
     i. **Adolescent or young males**
- Other vaccines: can be given without regard to timing of other vaccines

[1] Adapted from CDC Jynneos Vaccine

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Post-Exposure Prophylaxis

- Vaccination should be given **within 4 days** of known or presumed exposure
  a) 4-14 days following exposure: ↓ effectiveness
  b) >14 days following exposure: consider in certain situations
  c) **No benefit after symptom onset**
- ?Utility of vaccinia immune globulin (VIG)

[1] Adapted from CDC Vaccination Strategies

Conclusion

- MPXV has been around since 1958
- Primary mode of transmission via close contact
- Flu-like prodrome followed by characteristic rash
- Although low mortality, associated with significant morbidity
- Tecovirimat appears promising
- Vaccinations can reduce risk of developing MPXV

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New Pox on the Block: Understanding Monkeypox

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