Update on Human Mpox

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ADVAC Alumni Webinar
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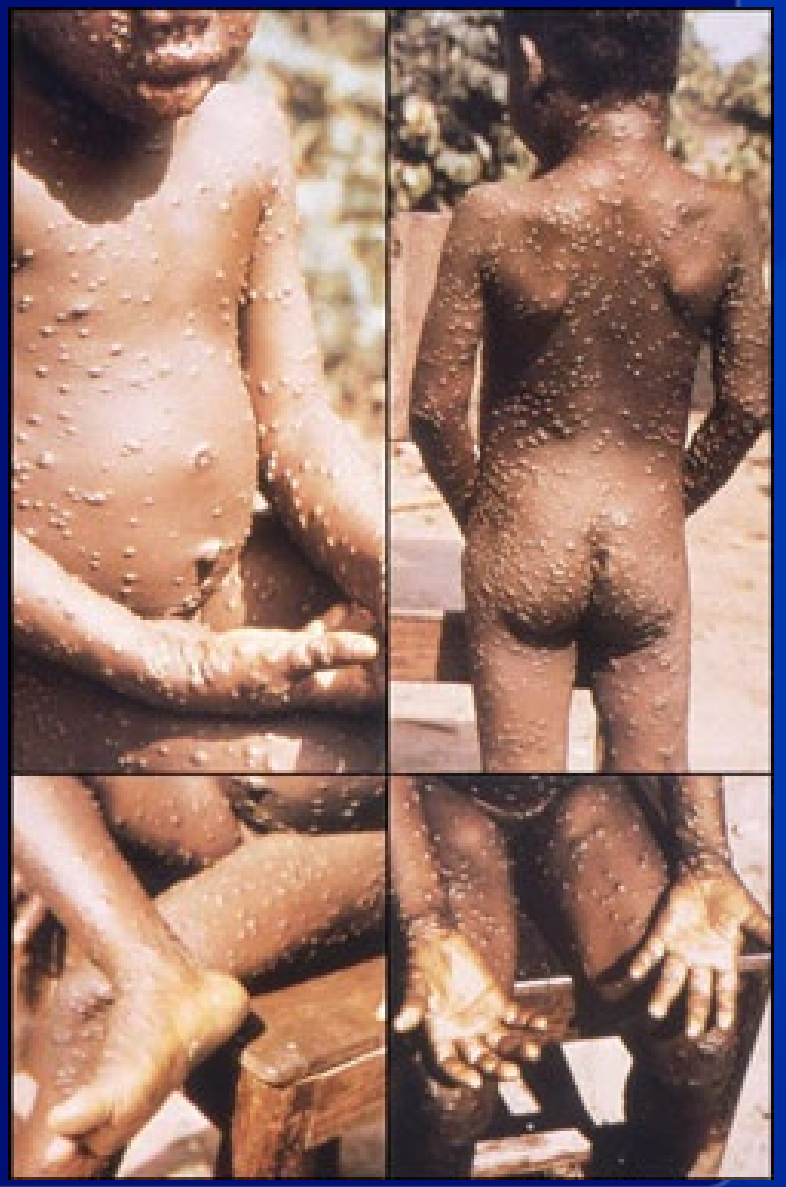
National Center for Emerging and Zoonotic Infectious Diseases
Division of High Consequence Pathogens and Pathology

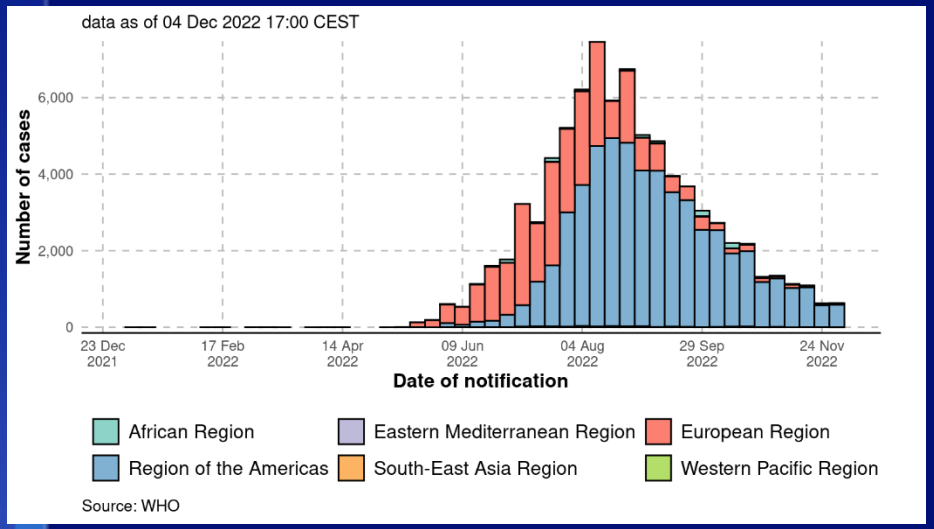
Mpox

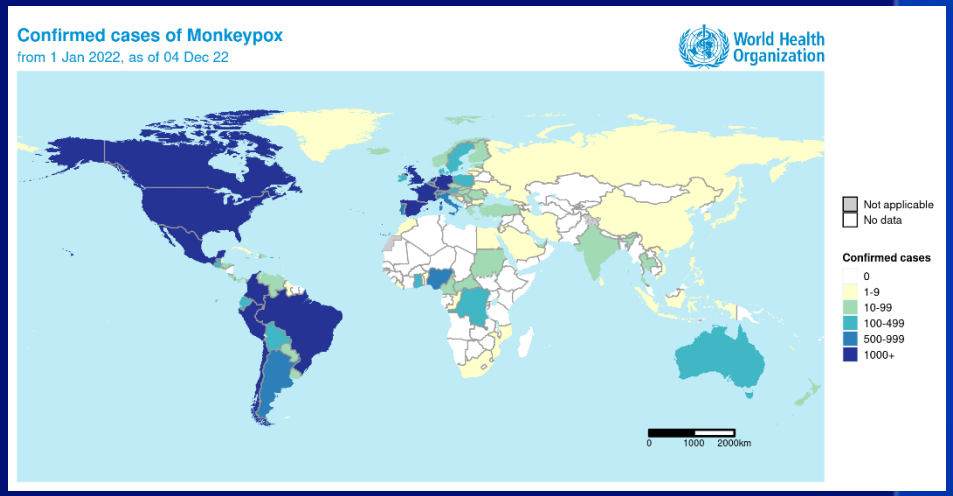
- **Causative agent: mpox virus**
  - Clade I (formerly Congo Basin)
  - Clade IIa (formerly West African)
  - Clade IIb (2022 outbreak)
- **Clinical presentation: disseminated vesicular/pustular rash associated with fever, malaise, and lymphadenopathy**
- **Transmission: zoonotic following contact with infected animals; human-to-human via respiratory droplets and lesion exudates; close contact during sexual activity**
- **Animal reservoir: likely small African rodents (rope squirrel, Gambian rat, dormouse)**



Global Mpox Outbreak

81,766	60	110
Confirmed cases	Deaths	Countries reporting cases





- First cases identified in May 2022
- On 23 July, 2022 WHO declared the global monkeypox outbreak to be a public health emergency of international concern (PHEIC)

https://worldhealthorg.shinyapps.io/mpx_global/

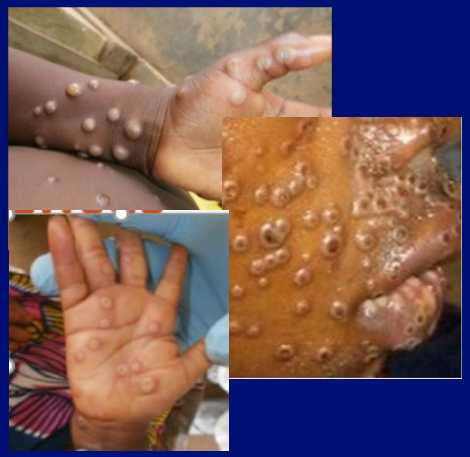
Mpox Outbreak Epidemiology

- 96.8% (45749/47250) male
- Median age is 34 years (IQR: 29 – 41)
- 86.1% (23810/27645) identified as men who have sex with men
- Male-to-male sexual contact (MMSC) most common route of transmission
- Some cases in women, children, and men who do not report recent MMSC

https://worldhealthorg.shinyapps.io/mpx_global/

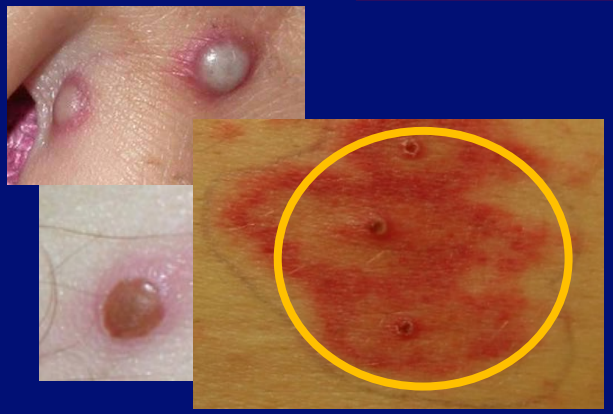
Clinical Presentation

1970–present
Countries endemic for monkeypox



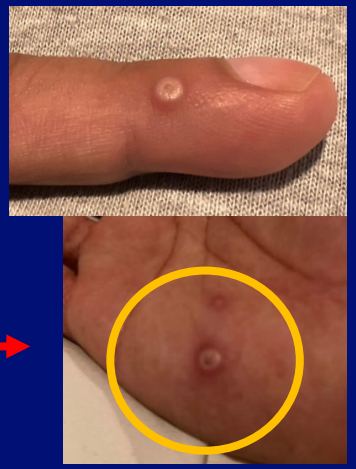
2003
United States

First lesion at site of exposure (bite or scratch)



2022
Globally

Small, localized lesions



- Firm, deep-seated, well circumscribed, painful, often umbilicated lesions
- Can involve palms and soles
- Associated with lymphadenopathy, fever, sore throat

Classic Mpox Vs. Current Cases

Characteristic	Classic Mpox	2022 outbreak
Zoonotic transmission	Yes	No
Person-to-person spread	Occurred but not well defined	Extensive in MSM networks
Location of lesions	Widespread rash, including on genitals	Localized or scattered rash, often limited to or involving genitals
Transmission		
Respiratory secretions (e.g., saliva)	Yes	Yes
Close skin-to-skin contact	Yes	Extensive
Fomites	Yes	Yes
Diagnosis		
Differential diagnosis	Chickenpox	Sexually transmitted infections, hand-foot-mouth disease, molluscum contagiosum, miscellaneous skin rash, bug bite, chickenpox
Co-infections	Yes (chickenpox)	Yes

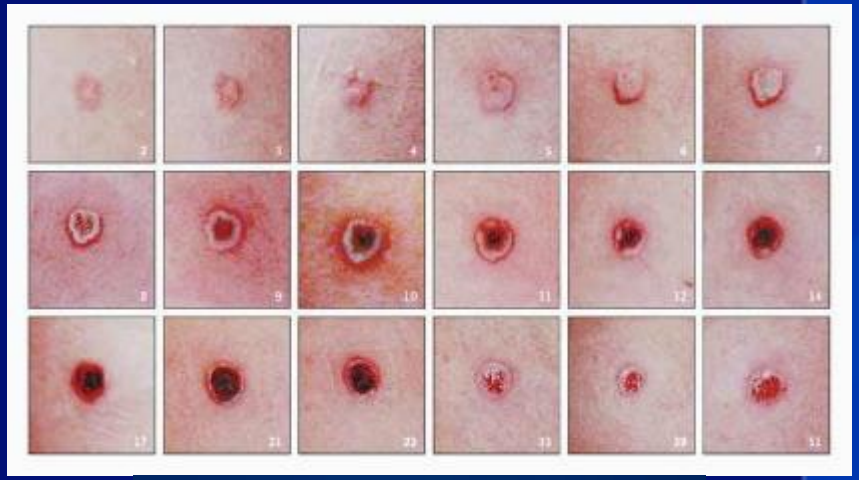
Prevention of Zoonotic Mpox

- Avoid contact with animals that could harbor the virus
- Isolate infected patients
- Use personal protective equipment (PPE) when caring for patients
- Practice good hand hygiene after contact with infected animals or humans

- Smallpox vaccination (administered 3–19 years previously) appeared to provide over 85% protection against disease acquisition in studies of close contacts of cases

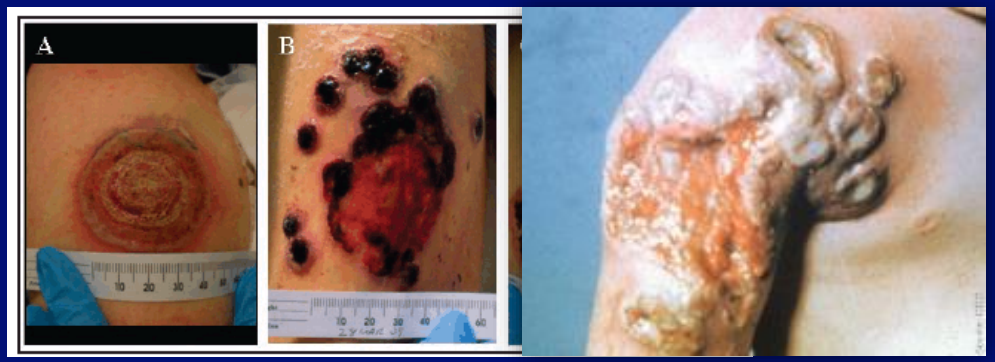
Traditional Smallpox Vaccines

- *Vaccinia virus*
- **Live virus, replication competent**
- **Administered via multiple puncture technique using a bifurcated needle**
- **Produces a major cutaneous reaction or "take"**
  - Evidence of successful vaccination

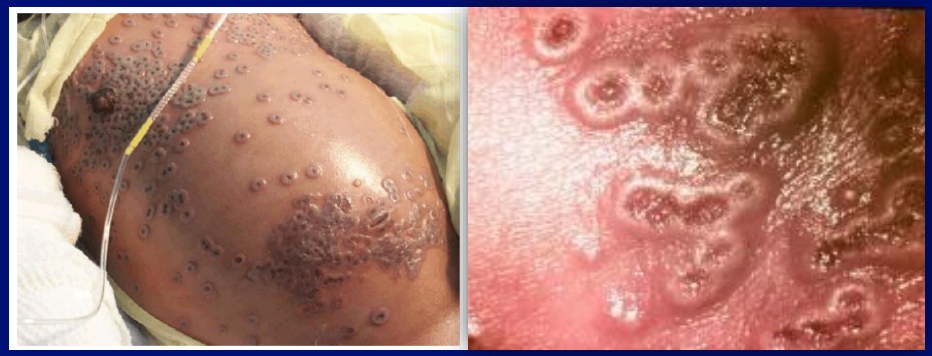


Severe Vaccinia Virus Complications

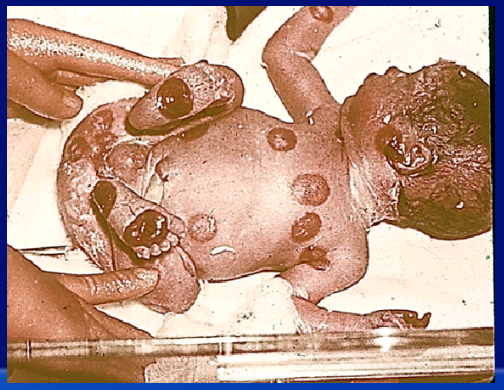
- Progressive vaccinia
- Eczema vaccinatum
- Postvaccinial encephalitis
- Autoinoculation / Inadvertent transmission
- Ocular infections
- Myopericarditis
- Fetal vaccinia
- Death



Progressive vaccinia



Eczema vaccinatum



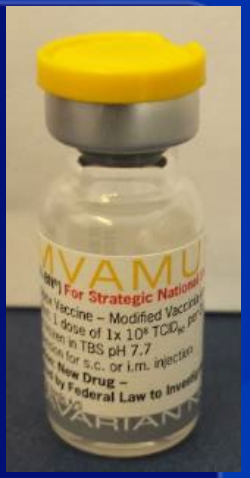
Fetal vaccinia

Ocular vaccinia

Smallpox Vaccine Advances

- 1st generation vaccines – propagated in calf skin
  - Dryvax, **Aventis Pasteur Smallpox Vaccine (APSV or Wetvax)**
- 2nd generation vaccines – propagated in tissue culture, produced using modern good manufacturing practices
  - **ACAM2000**
- 3rd generation vaccines – attenuated live virus propagated in tissue culture, produced using modern good manufacturing practices
  - **JYNNEOS/IMVAMUNE/IMVANEX**, LC16M8
- 4th generation vaccines – protein subunit vaccines, DNA vaccines
  - 4Pox

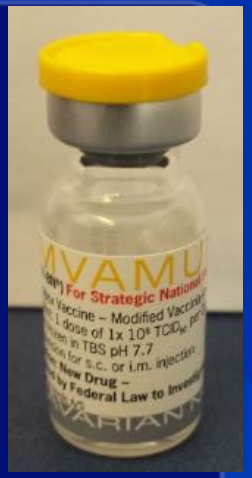
JYNNEOS



- **JYNNEOS is an attenuated, non-replicating live virus vaccine produced from the strain Modified Vaccinia Ankara-Bavarian Nordic (MVA-BN)**
  - Also known as IMVAMUNE, IMVANEX, MVA
- **Series of two doses administered 28 days (4 weeks) apart**
- **Tested in >7,000 human participants (including >400 HIV+ individuals and >380 individuals with atopic dermatitis)**
  - No severe adverse events
  - No vaccine site lesion or “take”
- **Licensed by FDA in September 2019 for prevention of smallpox and monkeypox disease in adults 18 years of age and older, licensed by EMA in July 2022 to protect adults from monkeypox and vaccinia virus disease**

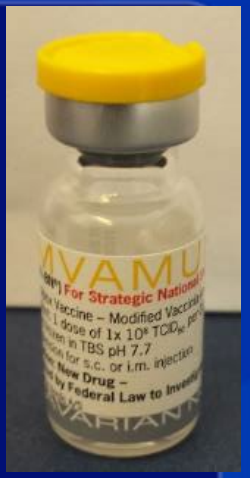
https://www.cdc.gov/poxvirus/monkeypox/interim-considerations/jynneos-vaccine.html

JYNNEOS Availability



- **Global supplies remain very limited**
- **Stockpiled for smallpox preparedness by some developed countries**
  - Early demand exceeded supply
- **PAHO's Revolving Fund has purchased 130,000 doses**
  - Countries and territories in Latin America and the Caribbean

JYNNEOS Administration



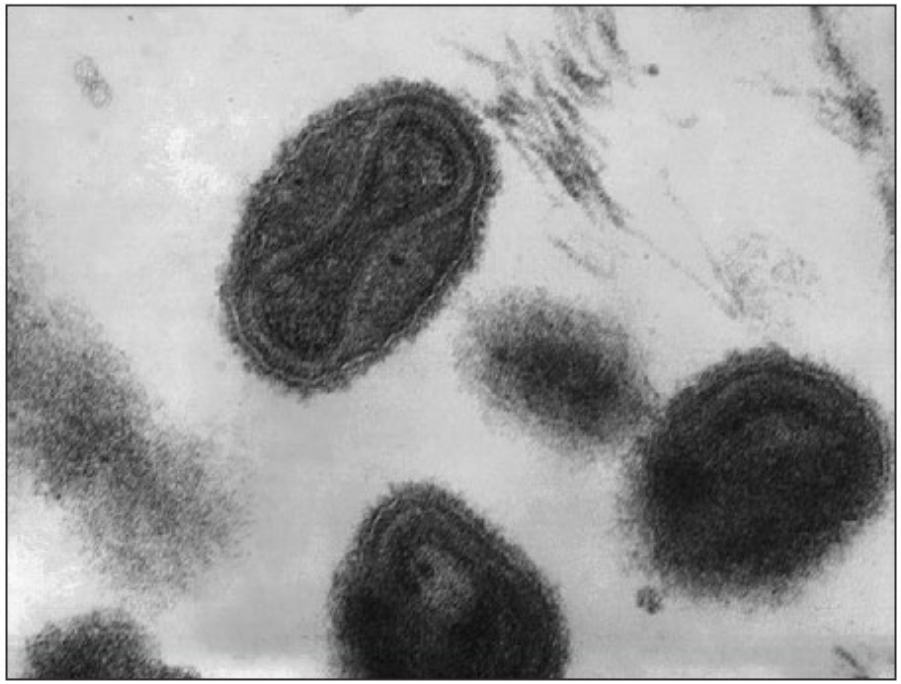
- **Standard regimen**
  - Subcutaneous administration – FDA licensed
    - Injection volume of 0.5mL
- **Alternative regimen**
  - Intradermal administration – FDA Emergency Use Authorization (EUA) for people >18 years
    - Injection volume of 0.1mL
  - The alternative regimen, when feasible, is preferred because this could increase the number of available vaccine doses
  - A clinical study showed that the lower intradermal dose was immunologically non-inferior to the standard SC regimen

https://www.cdc.gov/poxvirus/monkeypox/interim-considerations/jynneos-vaccine.html

Mpox Vaccination Strategy?

Centers for Disease Control and Prevention
MMWR
Morbidity and Mortality Weekly Report
Recommendations and Reports / Vol. 64 / No. 2
February 20, 2015

Clinical Guidance for Smallpox Vaccine Use in a Postevent Vaccination Program



U.S. National Monkeypox Vaccination Strategy

Component	Definition	Eligible Populations
Post-Exposure Prophylaxis (PEP)	Vaccination **after known exposure** to monkeypox	• People who are known contacts to someone with monkeypox who are identified by public health authorities, for example via case investigation, contact tracing, or risk exposure assessment
Expanded Post-Exposure Prophylaxis (PEP++)	Vaccination **after known or presumed** exposure to monkeypox	• People who are known contacts to someone with monkeypox who are identified by public health authorities, for example via case investigation, contact tracing, or risk exposure assessment • People who are aware that a recent sex partner within the past 14 days was diagnosed with monkeypox • Certain gay, bisexual, or other men who have sex with men, or transgender or nonbinary people, who have had any of the following within the past 14 days: sex with multiple partners (or group sex); sex at a commercial sex venue; or sex in association with an event, venue, or defined geographic area where monkeypox transmission is occurring

https://www.cdc.gov/poxvirus/monkeypox/interim-considerations/overview.html

U.S. National Monkeypox Vaccination Strategy

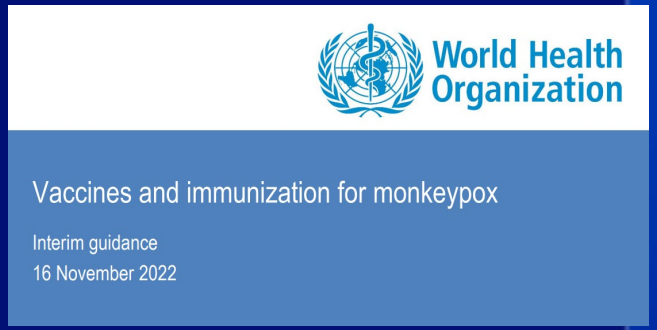
Component	Definition	Eligible Populations

Pre-Exposure Prophylaxis (PrEP)	Vaccination **before exposure** to monkeypox	• People in certain occupational exposure risk groups
		• Gay, bisexual, and other men who have sex with men, transgender or nonbinary people who in the past 6 months have had
		  • A new diagnosis of one or more nationally reportable sexually transmitted diseases (i.e., acute HIV, chancroid, chlamydia, gonorrhea, or syphilis)
		  • More than one sex partner
		• People who have had any of the following in the past 6 months:
		  • Sex at a commercial sex venue
		  • Sex in association with a large public event in a geographic area where monkeypox transmission is occurring
		• Sexual partners of people with the above risks
		• People who anticipate experiencing the above risks

https://www.cdc.gov/poxvirus/monkeypox/interim-considerations/overview.html

WHO Interim Guidance for Vaccines

- **Primary preventive (pre-exposure) vaccination (PPV)**
  - PPV is recommended for individuals at high-risk of exposure. Persons at highest risk of exposure in the current multi-country outbreak are gay, bisexual or other men who have sex with men (MSM) with multiple sexual partners.
  - Others at risk may include individuals with multiple casual sexual partners; sex workers; health workers at risk of repeated exposure, laboratory personnel working with orthopoxviruses; clinical laboratory and health care personnel performing diagnostic testing for monkeypox; and outbreak response team members.
- **Post-exposure preventive vaccination (PEPV) is recommended for contacts of cases ideally within four days of first exposure (and up to 14 days in the absence of symptoms).**

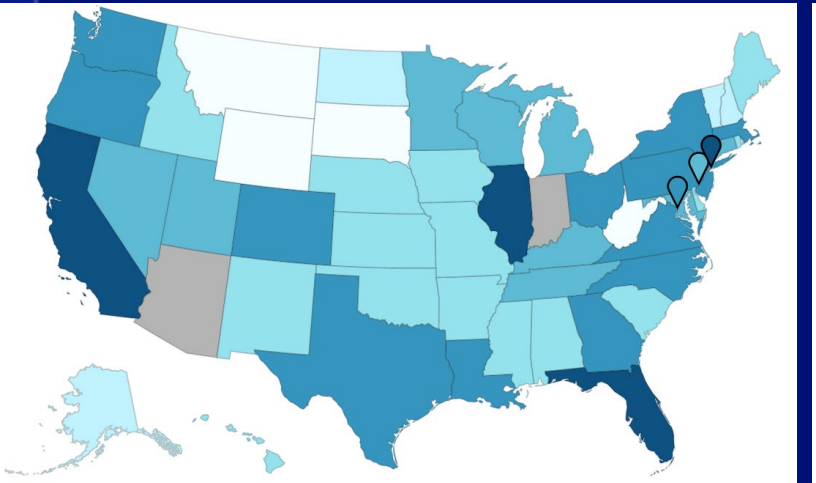


https://www.who.int/publications/i/item/WHO-MPX-Immunization

Total JYNNEOS Vaccine Doses Administered and Reported to CDC

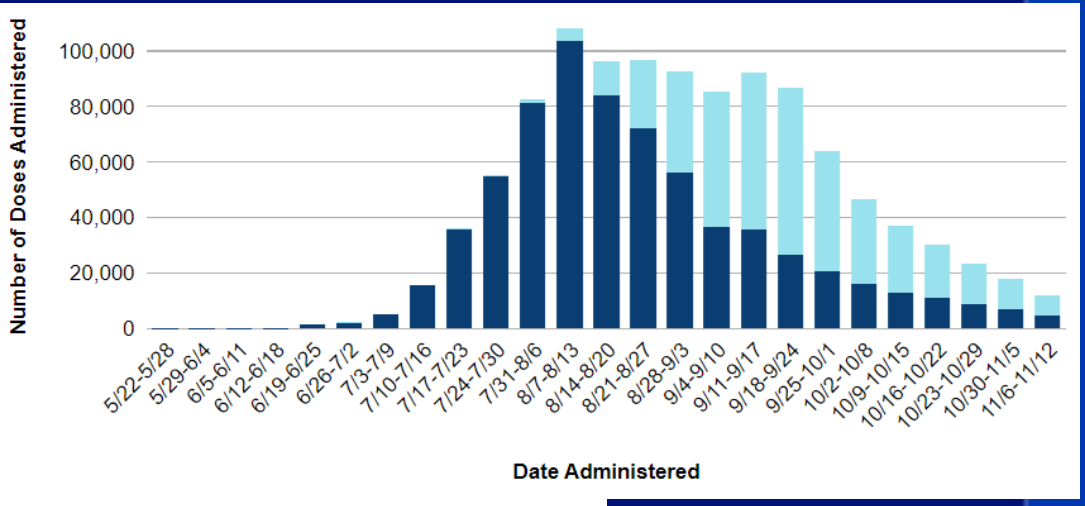
1,090,222

Doses Administered in the 57 U.S. Jurisdictions Reporting Data as of November 15, 2022.



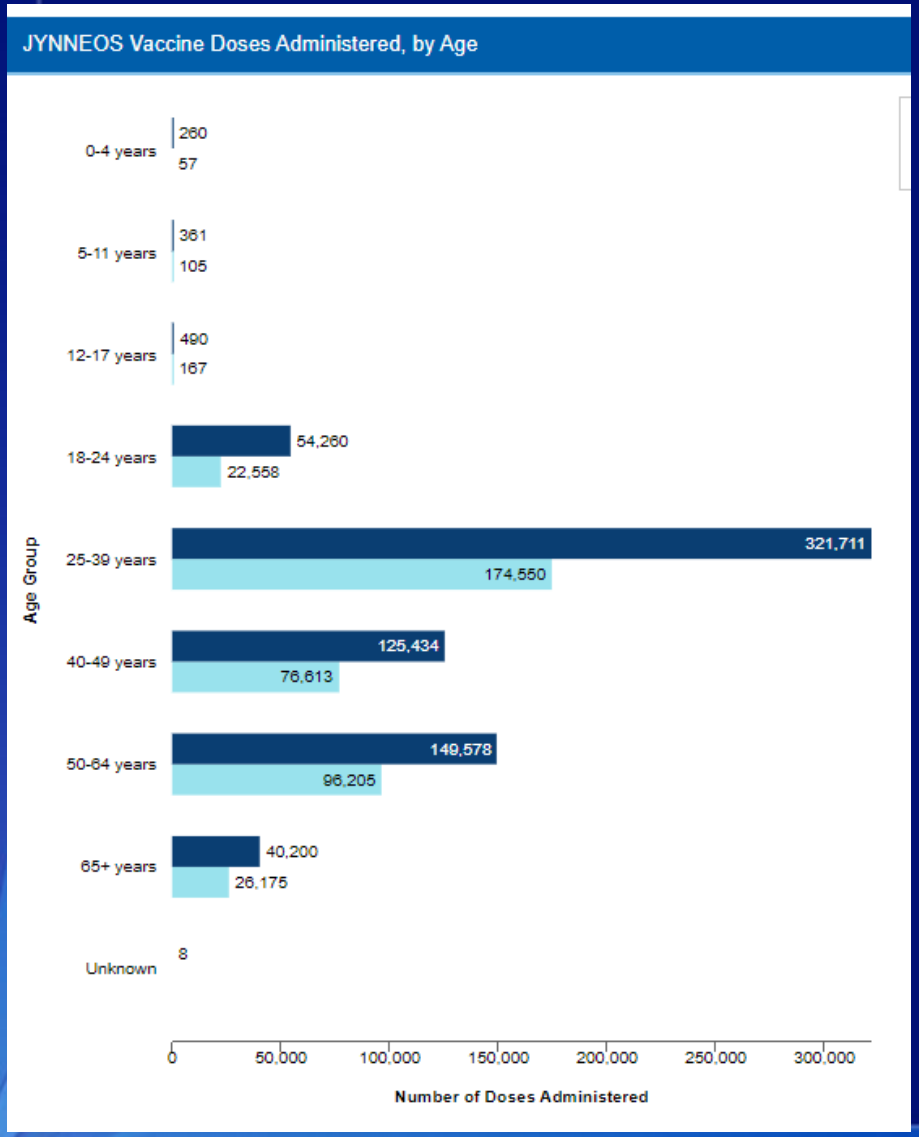
Doses Administered

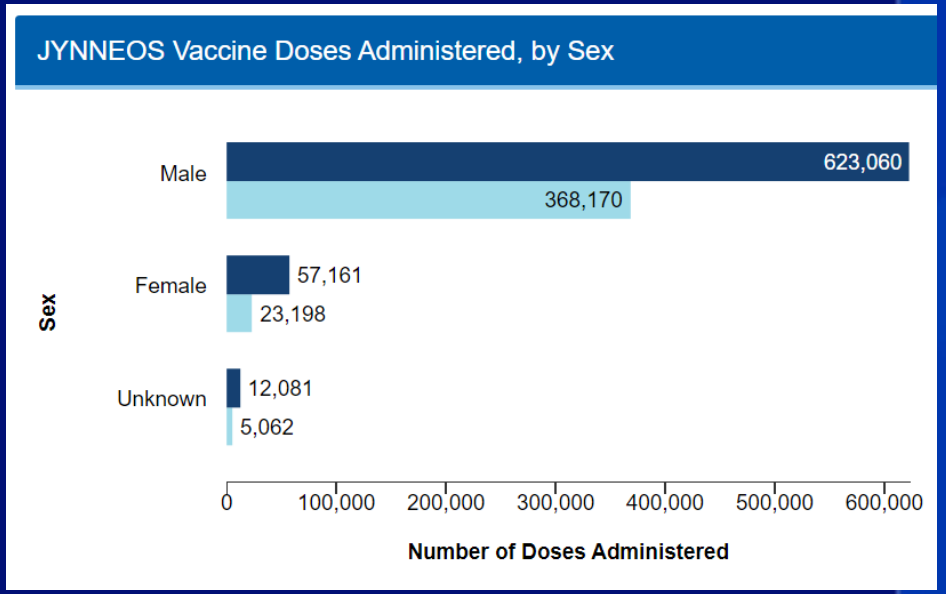
- Data not yet reported to CDC
- 1 - 500
- 501 - 1,000
- 1,001 - 5,000
- 5,001 - 10,000
- 10,001 - 50,000
- > 50,000

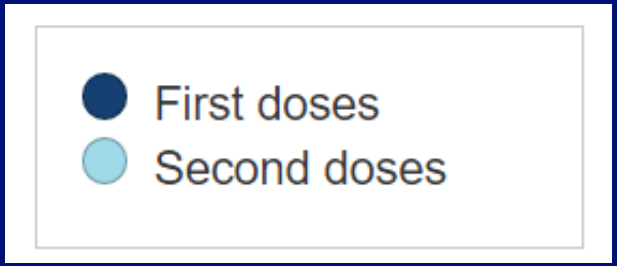


https://www.cdc.gov/poxvirus/monkeypox/response/2022/vaccines_data.html

Total JYNNEOS Vaccine Doses Administered and Reported to CDC

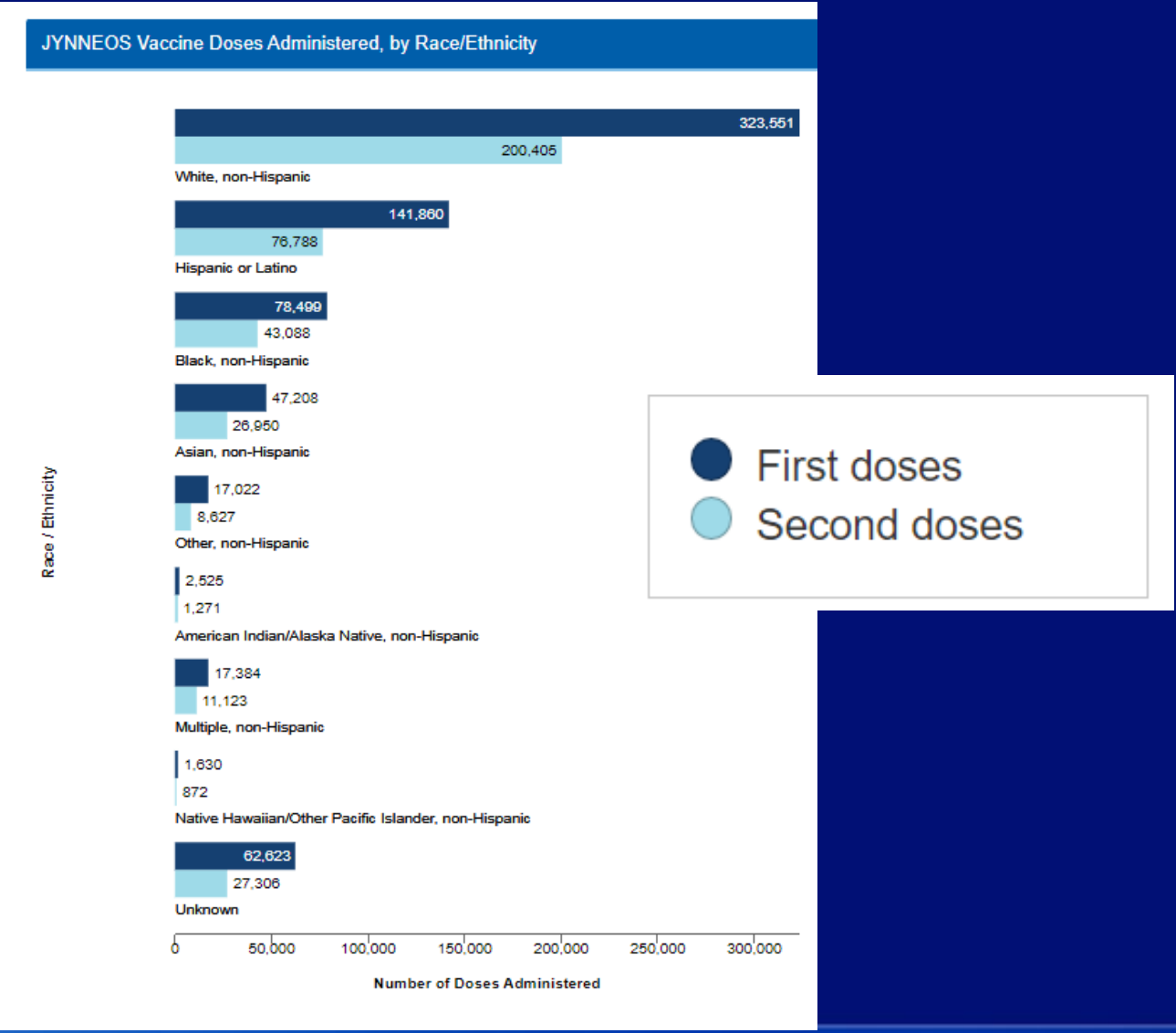






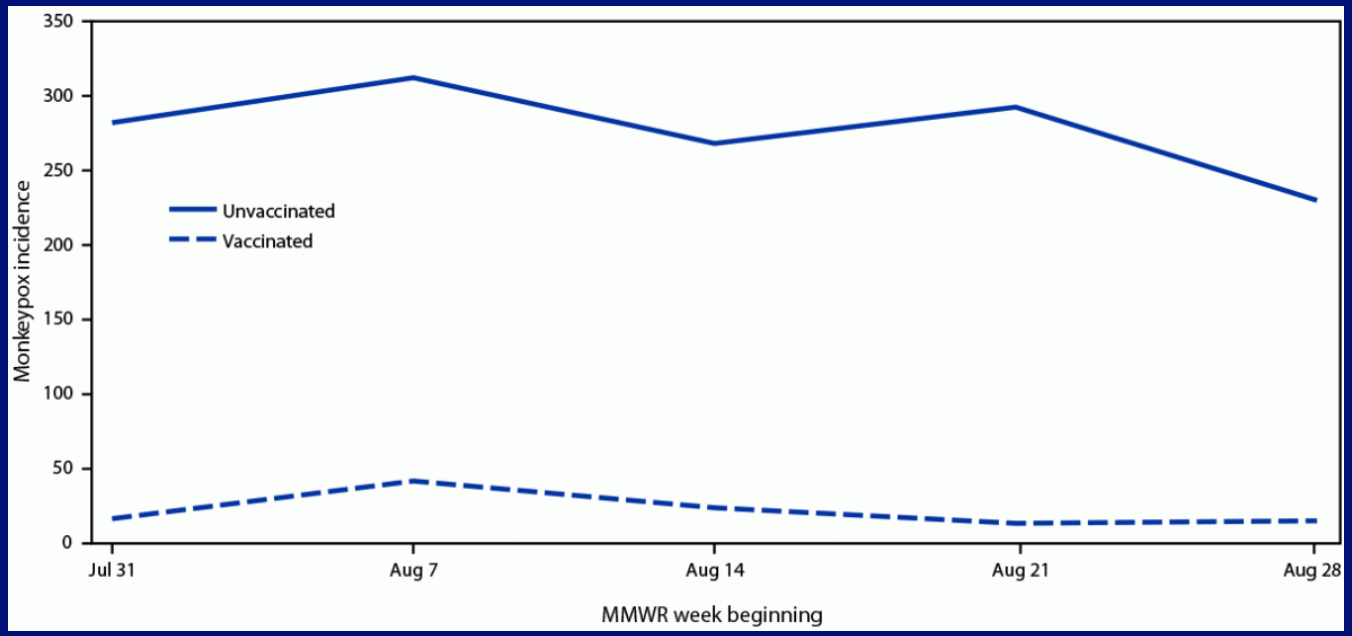
https://www.cdc.gov/poxvirus/monkeypox/response/2022/vaccines_data.html

Total JYNNEOS Vaccine Doses Administered and Reported to CDC



https://www.cdc.gov/poxvirus/monkeypox/response/2022/vaccines_data.html

Incidence of Monkeypox Among Unvaccinated Persons Compared with Persons Receiving ≥1 JYNNEOS Vaccine Dose — 32 U.S. Jurisdictions, July 31–September 3, 2022



- 5,402 reported monkeypox cases occurring among males aged 18–49 years were analyzed by vaccination status across 32 U.S. jurisdictions
- Monkeypox incidence was 14 times as high among unvaccinated males compared with those who had received a first vaccine dose ≥14 days earlier

https://www.cdc.gov/mmwr/volumes/71/wr/mm7140e3.htm

JYNNEOS Effectiveness

- **Effectiveness of a single-dose Modified Vaccinia Ankara in Human Monkeypox: an observational study**
  - 1,970 subjects met the study eligibility criteria
  - 873 (44%) were vaccinated with MVA and completed at least 25 days of follow-up
  - 18 infections were confirmed during the study period, 3 in vaccinated and 15 in unvaccinated status
  - VE was estimated at 79% (95% CI: 24%-94%)
- **Breakthrough infections after post-exposure vaccination against Monkeypox**
  - 276 individuals received one dose of IMVANEX® with a median delay of 11 days [IQR 8-14] after exposure with a confirmed Monkeypox patient
  - 12 (4%) had a confirmed Monkeypox breakthrough infection with no severe infection

https://www.researchsquare.com/article/rs-1976861/v2

https://www.medrxiv.org/content/10.1101/2022.08.03.22278233v1

Treatment Considerations for Mpox

- **Most immunocompetent patients recover with pain management and other supportive care**
- **Tecovirimat should be considered for some conditions**
  - **Severe disease** - Hemorrhagic disease, large number of lesions, sepsis, encephalitis, ocular or periorbital infections, other conditions requiring hospitalization
  - Lesions involving **anatomic areas that could cause serious sequelae that include scarring or strictures** (e.g., pharynx, penile foreskin, vulva, vagina, urethra, anus)
  - Lesions in people who are at **high risk for severe disease**
    - Immunocompromised individuals
    - Pediatric populations
    - Pregnant or breastfeeding people
    - People with conditions affecting skin integrity

https://www.cdc.gov/poxvirus/monkeypox/clinicians/treatment.html

Tecovirimat

- **Tecovirimat (TPOXX or ST-246) is an antiviral medication developed to treat smallpox**
- **Oral capsule and IV formulations approved by FDA in July 2018 and May 2022, respectively**
- **Indication**
  - Tecovirimat is indicated for the treatment of human smallpox disease in adults and pediatric patients weighing at least 3 kg
  - CDC-held Expanded Access Investigational New Drug (EA-IND) Protocol allows use for Non-Variola Orthopoxvirus infection (e.g., monkeypox)
- **Available from the United States Strategic National Stockpile**
- **6,293 patients prescribed or treated with Tecovirimat in the U.S.**

https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/208627s000lbl.pdf

Other Treatment Options

- Cidofovir (also known as Vistide) is an antiviral medication that is used for the treatment of cytomegalovirus (CMV) retinitis

- Brincidofovir (also known as CMX001 or Tembexa) is an antiviral medication that was approved by the FDA for the treatment of human smallpox disease

- Vaccinia Immune Globulin Intravenous (VIGIV) is licensed by FDA for the treatment of complications due to vaccinia vaccination

- Trifluridine (also known as Viroptic) is an antiviral medication licensed for the treatment of herpes keratoconjunctivitis/keratitis

https://www.fda.gov/vaccines-blood-biologics/approved-blood-products/vaccinia-immune-globulin-intravenous-human
https://www.accessdata.fda.gov/drugsatfda_docs/label/1999/020638s003lbl.pdf
https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/214460s000,214461s000lbl.pdf
https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=abc1d07f-91ee-4421-bc9b-457d0ed41f4c

Summary

- **Ongoing global outbreak, predominantly affecting MSM**
  - Sexual contact most common route of transmission
  - No sustained transmission in communities outside of MSM networks
- **Severe cases and deaths among people who are immunocompromised**
- **Vaccines available for prevention**
  - Vaccine efficacy not defined for mpox
  - Outstanding questions
- **Therapeutics available for treatment**
  - Effectiveness not proven
  - Optimal clinical utilization uncertain

Questions?

For more information please contact Centers for Disease Control and Prevention

Telephone: 1-800-CDC-INFO (232-4636)/TTY: 1-888-232-6348

E-mail: cdcinfo@cdc.gov Web: http://www.cdc.gov

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

Occupational Considerations for Monkeypox Vaccine

- **At this time, most clinicians in the United States and laboratorians not performing the orthopoxvirus generic test to diagnose orthopoxviruses, including monkeypox, are not advised to receive orthopoxvirus PrEP**
- **People who should get PrEP include:**
  - Clinical laboratory personnel who perform testing to diagnose orthopoxviruses, including those who use polymerase chain reaction (PCR) assays for diagnosis of orthopoxviruses, including Monkeypox virus
  - Research laboratory workers who directly handle cultures or animals contaminated or infected with orthopoxviruses that infect humans, including Monkeypox virus, replication-competent Vaccinia virus, or recombinant Vaccinia viruses derived from replication-competent Vaccinia virus strains
  - Certain healthcare and public health response team members designated by public health authorities to be vaccinated for preparedness purposes

https://www.cdc.gov/poxvirus/monkeypox/clinicians/smallpox-vaccine.html

ACTG AIDS CLINICAL TRIALS GROUP

STOMP

Study of Tecovirimat for Human Monkeypox Virus

IMPAACT International Maternal Pediatric Adolescent AIDS Clinical Trials Network

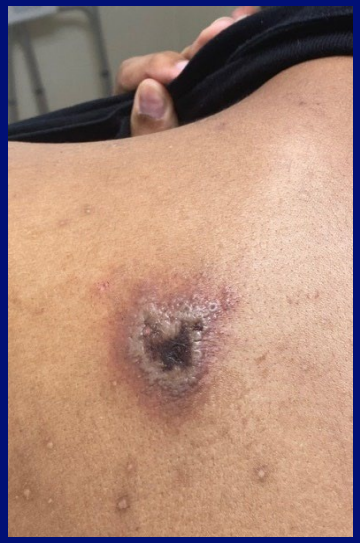
- **Study Population: Symptomatic monkeypox virus infection**
- **Randomized Arms: Tecovirimat vs. placebo (2:1)**
  - Primary efficacy objective: To show that Tecovirimat reduces time to clinical resolution.
  - If progressing to severe or experiencing severe pain, then can move to open-label Tecovirimat
- **Open Label Tecovirimat Arm**
  - Severe disease (hospitalized, ocular disease, facial lesions, complicated ulcers)
  - Children, pregnant and breastfeeding people
  - Severe skin disease or immune suppression
- **In-person enrollment, then 8 weeks virologic assessments, daily diary, and telemedicine (Completely remote option is forthcoming)**

STOMPTPOXX.ORG	(855) 876-9997	NCT05534984
Website with list of active sites	Call center to connect to sites	See clinicaltrials.gov for details

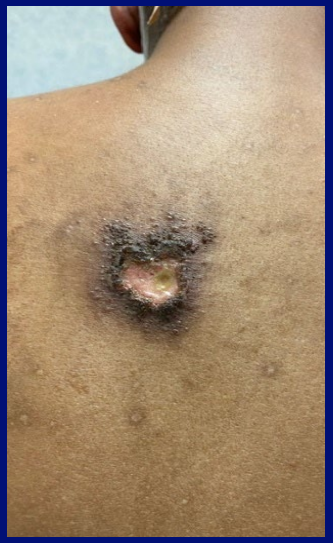
https://clinicaltrials.gov/ct2/show/NCT05534984

Severe Manifestations of Monkeypox

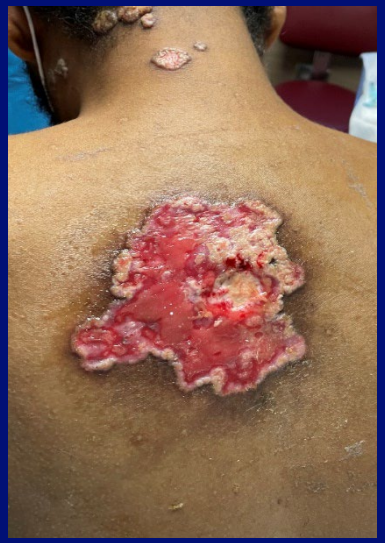
- Atypical or persistent rash with coalescing or necrotic lesions, or both
- Lesions on a significant proportion of the total body surface area
- Certain lesions in sensitive areas (such as face, genitalia, bowel, urethra)
- Lesions associated with edema and secondary bacterial or fungal infections
- Severe lymphadenopathy
- Lesions leading to stricture, scar formation, obstruction



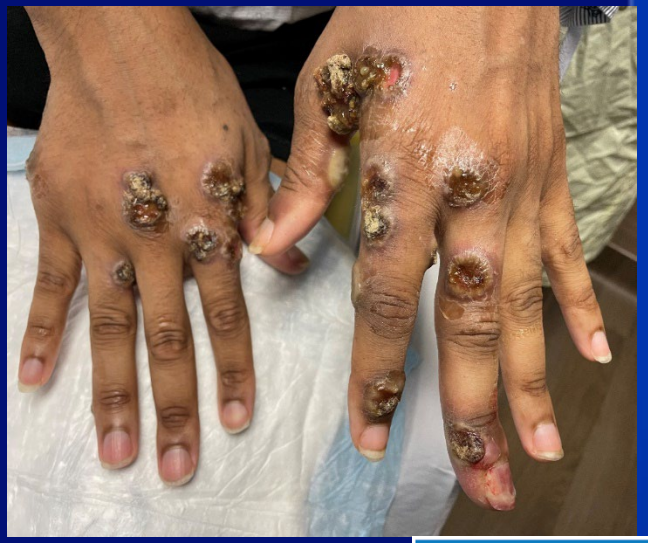
Upon presentation



13 days of oral tecovirimat



Outpatient follow up



https://emergency.cdc.gov/han/2022/han00475.asp

https://emergency.cdc.gov/coca/calls/2022/callinfo_100622.asp

COCA

HAN

HEALTH ALERT NETWORK

Severe Manifestations of Monkeypox

- **Optimize immune function among immunocompromised people with suspected or confirmed monkeypox**
  - Ensure those with HIV are on effective antiretroviral therapy
- **Consider treating immunocompromised people diagnosed with monkeypox with tecovirimat as early as possible in the course of disease and consider a prolonged course of tecovirimat for those with more refractory and severe monkeypox infection**
- **Have a low threshold to use multiple medical countermeasures for people with severe manifestations of monkeypox or people who are at high risk of progression to severe manifestations**

https://emergency.cdc.gov/han/2022/han00475.asp

HAN
HEALTH ALERT NETWORK

Smallpox Research Agenda

- **The goal of the smallpox research is to address three areas that are essential for public health:**
  - Finding better antiviral drugs to treat smallpox disease
    - Tecovirimat, Brincidofovir
  - Making safer vaccines
    - Jynneos, ACAM2000
  - Improving tests to detect variola virus
    - FDA 510(k) cleared Non-variola Orthopoxvirus Real-time PCR assay

World Health Organization

BIOMEDICAL ADVANCED RESEARCH AND DEVELOPMENT AUTHORITY BARDA

CDC CENTERS FOR DISEASE CONTROL AND PREVENTION

FDA

NIH

https://www.cdc.gov/smallpox/research/index.html