Monkeypox Treatment and Prevention

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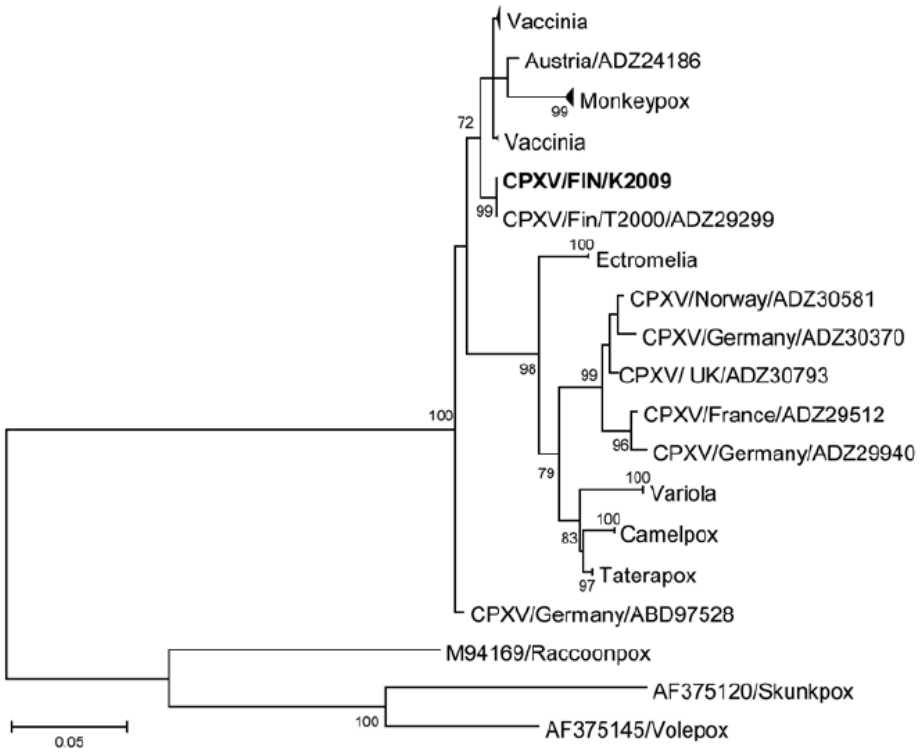
Disclosures

- **The speaker is a consultant to and has received honoraria and/or research support from the following companies:**
  - Atea
  - Decoy
  - Gilead
  - GlaxoSmithKline
  - Janssen
  - Merck
  - Moderna
  - Novartis
  - Pfizer
  - Shinogi
  - ViiV
  - Virostatics

Overview

- **Monkeypox is a member of the Orthopox genus of viruses belonging to the Poxviridae family**
  - Closely related to smallpox (variola), cowpox, vaccinia, canarypox, etc.



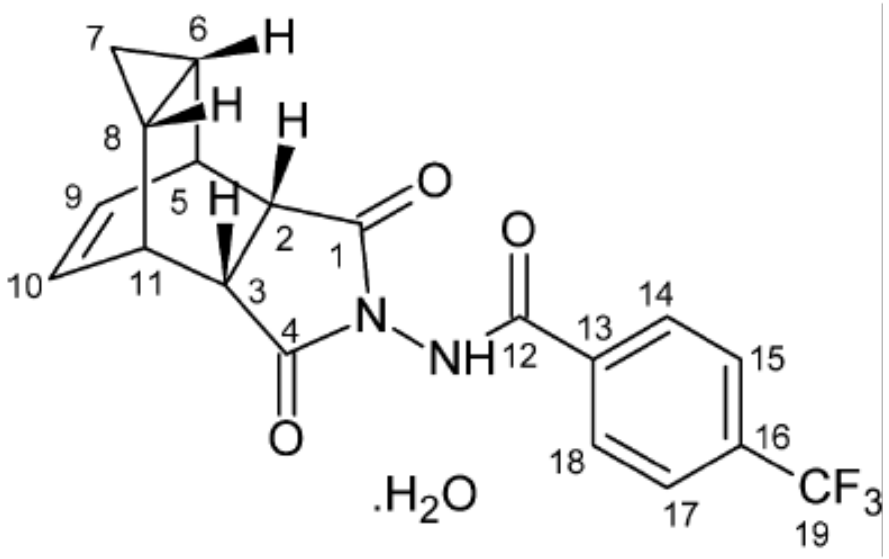
Current status of treatment and prevention of smallpox virus

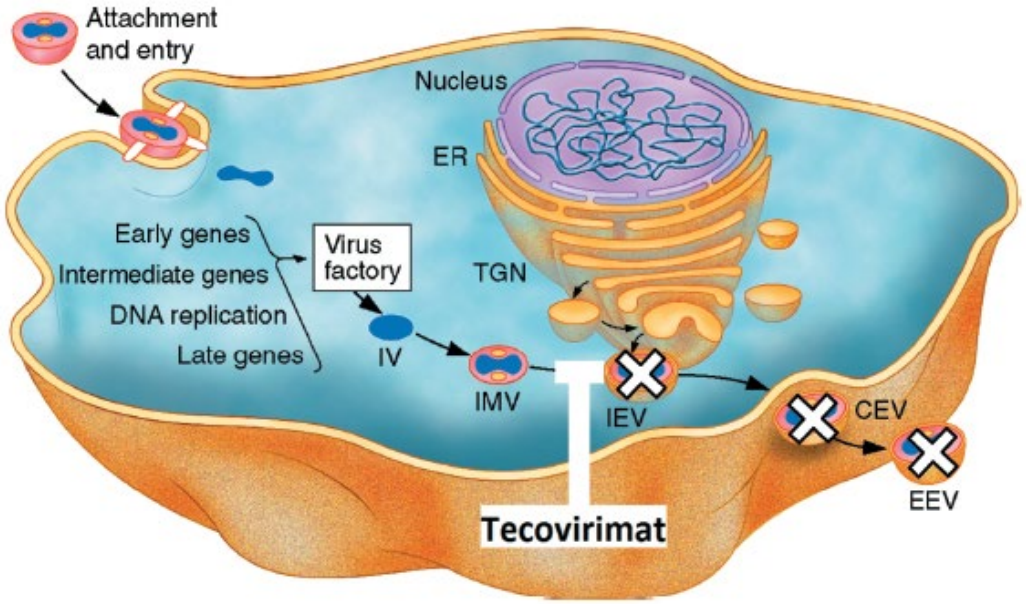
- **Three US FDA-approved drugs for treatment of smallpox virus**
  - Tecovirimat
  - Cidofovir
  - Brincidofovir
- **Two US FDA vaccines approved for prevention of smallpox:**
  - ACAM2000
  - Jynneos
- **Approval of these drugs/vaccines has been based on the "animal rule"**
  - allows approval of drugs for human use based on results of appropriate animal trials when clinical trials in humans cannot be conducted
- **Prior to the current outbreak, experience with these agents for treatment and/or prevention of monkeypox was scant**

Treatment

Tecovirimat (TPOXX; ST-246)

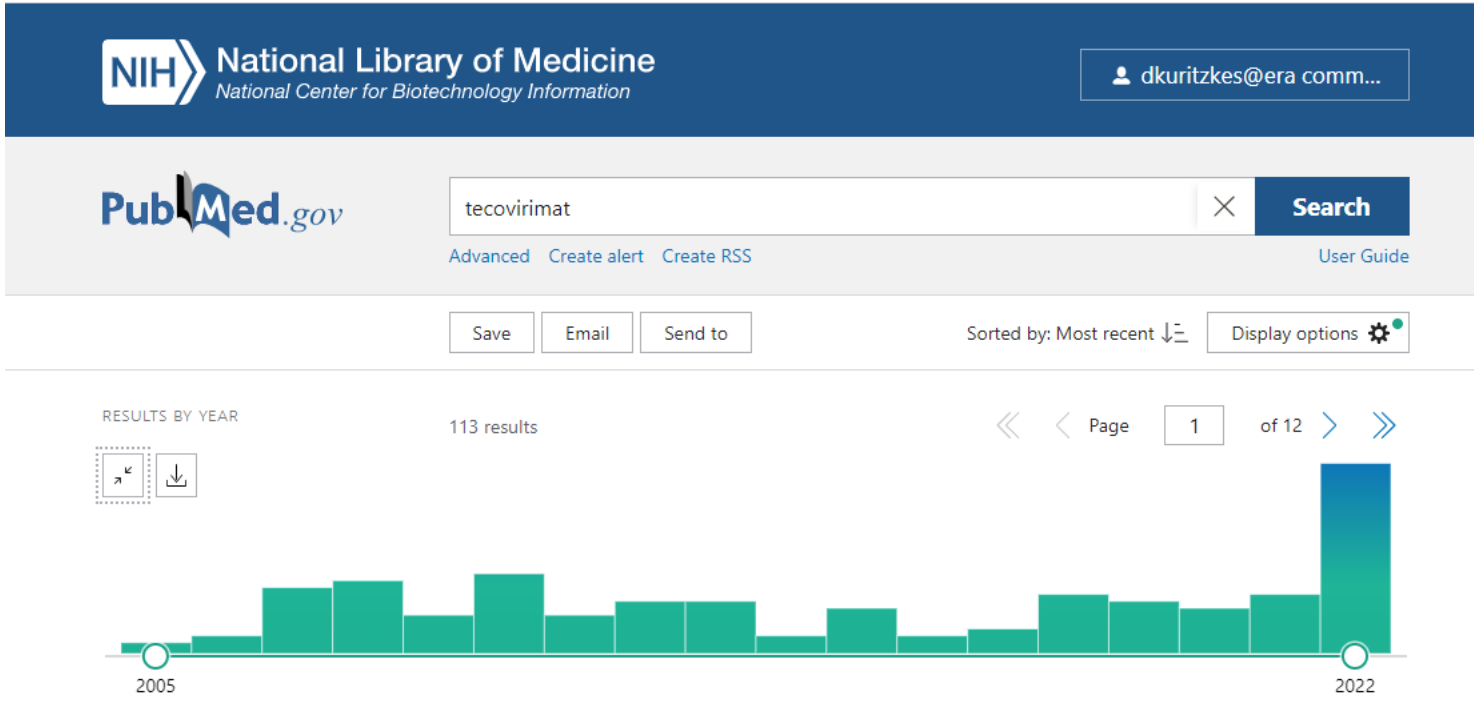
- Approved for treatment of smallpox in 2018
- Targets VP37, which is required for envelopment of intracellular mature virus by Golgi-associated membranes
- Broadly active against Orthopoxviridae





Russo AT et al Expert Rev of Anti-Infective Ther 2019

Number tecovirimat citations in PubMed (30 Aug)



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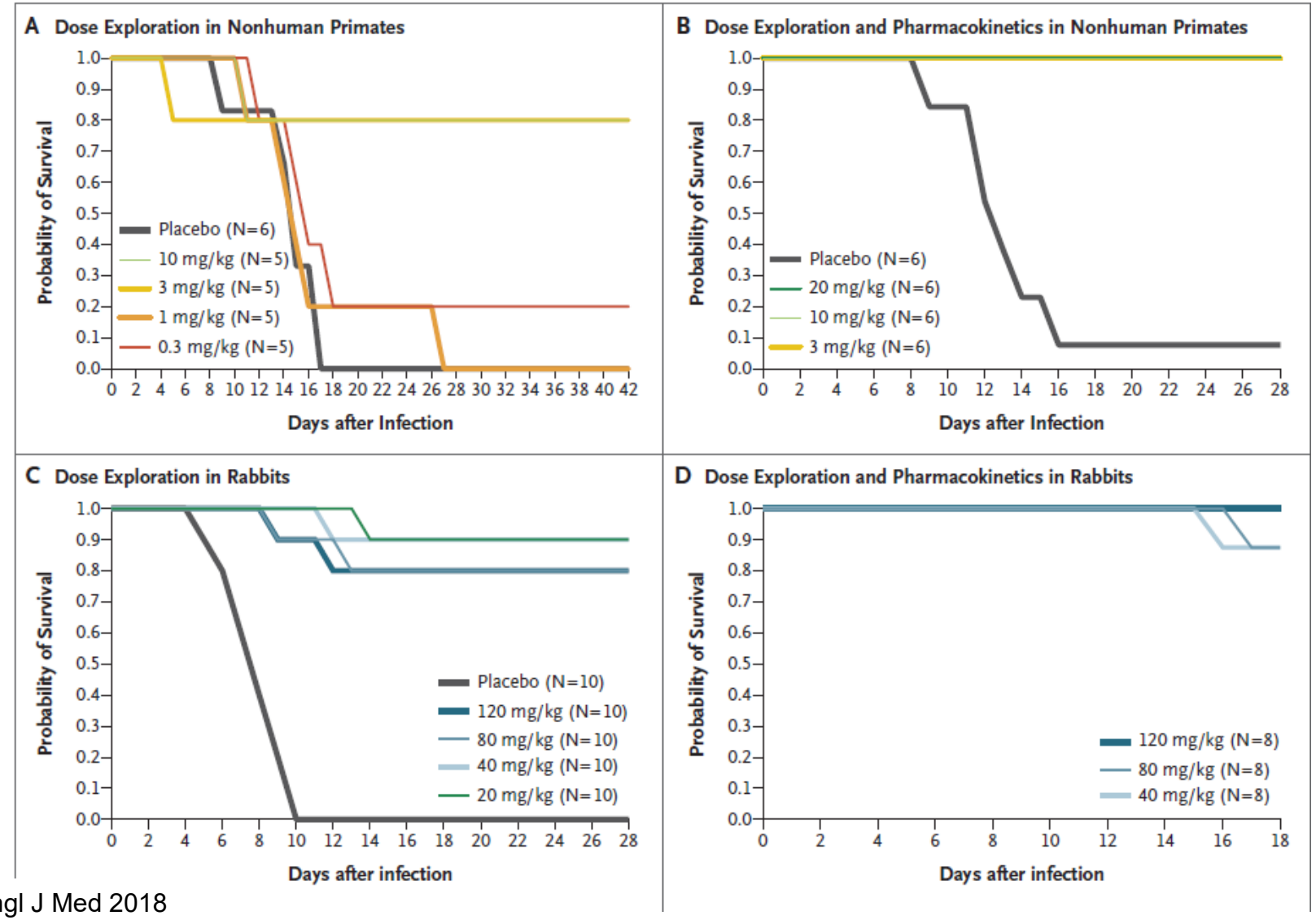
Activity of tecovirimat in rabbit- and monkeypox models of infection



Grossenbach DW et al N Engl J Med 2018

Tecovirimat adverse events in human PK study

Type of Event*	Placebo (N=90)		Tecovirimat (N=359)		Total (N=449)	
	No. of Participants (%)	No. of Events	No. of Participants (%)	No. of Events	No. of Participants (%)	No. of Events
Any event	30 (33.3)	68	134 (37.3)	318	164 (36.5)	386
Event related to the trial agent	15 (16.7)	32	71 (19.8)	176	86 (19.2)	208
Event leading to discontinuation of trial agent	2 (2.2)	3	6 (1.7)	16	8 (1.8)	19
Serious events and events leading to death	0	0	1 (0.3)†	1	1 (0.2)	1

Grossenbach DW et al N Engl J Med 2018

Human clinical experience with tecovirimat

- Most experience with tecovirimat has been in treatment of severe or disseminated vaccinia virus infection[1-3]
- Accumulating anecdotal experience in treatment of monkeypox[4-6]
- A randomized clinical trial sponsored by NIAID is being conducted by the ACTG (A5418)

[1]Lederman ER et al J Infect Dis 2012; Kinnunen PM et al Emerg Infect Dis 2015; Whitehouse ER MMWR 2019
[2]Adler H et al JAMA 2022; Desai A et al Ann Intern Med 2022; Matias W et al OFID 2022; Lucar J et al Ann Intern Med 2022; Sherwat et al N Engl J Med 2022

Cidofovir and brincidofovir

- **Phosphonate nucleotide analog inhibitors of DNA polymerase with broad activity against dsDNA viruses**
  - CMV, adenovirus, Ebola, orthopoxviruses
- **Approved for treatment of smallpox under the "animal rule"[1]**
- **Cidofovir must be administered intravenously; dose-limiting nephrotoxicity**
- **Brincidofovir is an orally available prodrug of cidofovir with reduced nephrotoxicity**
  - Phase 2 trials showed reduced risk of CMV in stem cell transplant recipients; phase 3 trials showed excess mortality and trials for CMV and adenovirus were halted[2]
  - Anecdotal reports of treatment of disseminated vaccinia and monkeypox[3]
  - Current availability for monkeypox limited

[1]Chen-Tack K et al Antiviral Res 2021
[2]Marty FM et al N Engl J Med 2013; Marty FM et al Biol Blood Marrow Transplant 2019
[3]Lederman ER et al J Infect Dis 2012; Adler H et al JAMA 2022; Volar S et al Clin Infect Dis 2008

CDC Interim Clinical Guidance for the Treatment of Monkeypox

- **People with severe disease**
- **People who may be at high risk of severe disease:**
  - People with immunocompromise
  - Pediatric populations, particularly patients younger than 8 years of age
  - People with a history or presence of atopic dermatitis or other active exfoliative skin conditions
  - Pregnant or breastfeeding women
- **People with one or more complications**
- **People with monkeypox virus aberrant infections that include accidental implantation in eyes, mouth, or other anatomical areas where monkeypox virus infection might constitute a special hazard (e.g., the genitals or anus)**

Source: https://www.cdc.gov/poxvirus/monkeypox/clinicians/treatment.html Accessed 21 August 2022

Tecovirimat prescribing information

- **Dosing: 600 mg (3 x 200 mg capsules) po BID for 14 days**
  - Pediatric dosing is available for children
  - IV formulation available
- **Adverse Reactions**
  - Oral: headache (12%), nausea (5%), abdominal pain (2%), and vomiting (2%). Neutropenia was found in one study participant.
  - IV: infusion site pain (73%), infusion site swelling (39%), infusion site erythema (23%), infusion site extravasation (19%), and headache (15%)
- **Cautions**
  - Do not administer to patients with severe renal impairment (CrCl <30mL/min).
  - Use with caution in persons with mild to moderate renal impairment and in children under 2 years of age
  - Weak inducer of CYP3A4; potential drug-drug interactions with certain ARVs

Source: https://www.cdc.gov/poxvirus/monkeypox/clinicians/Tecovirimat.html; https://hiv-druginteractions.org/checker Accessed 31 August 2022

Prevention

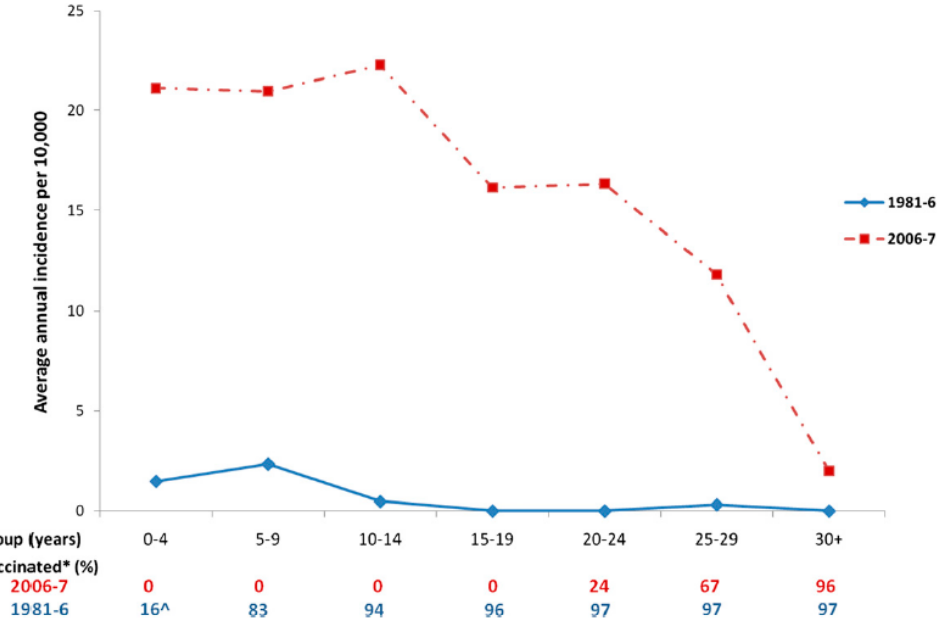
Vaccines to prevent smallpox

- **ACAM2000 is a replication-competent, live-virus vaccine**
  - Risk of eczema vaccinatum in persons with atopic dermatitis; dissemination in immunocompromised patients; myocarditis
  - Animal models show protection against monkeypox; no human data
- **Jynneos is a replication-defective, live-virus vaccine**
  - No risk of dissemination
  - Animal models show protection against monkeypox; no human data
- **Retrospective data correlating a rise in monkeypox cases in the Congo to cessation of smallpox vaccination suggest a protective effect of smallpox vaccine against monkeypox[1]**

[1]Rimoin AW et al Proc Nat Acad Sci (USA) 2010

Association of smallpox vaccination and monkeypox in the Congo

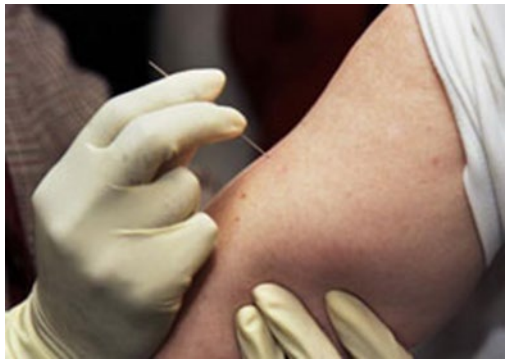
	Unvaccinated*			Vaccinated			Unvaccinated vs. vaccinated		
Age group	MPX† cases	Incidence‡	95% CI§	MPX cases	Incidence‡	95% CI§	Incidence ratio¶	95% CI§	*P* values
>0–4	185	8.87	7.68–10.24	—	—	—	—	—	—
5–9	167	7.06	6.07–8.22	—	—	—	—	—	—
10–14	185	9.35	8.10–10.80	—	—	—	—	—	—
15–19	96	7.03	5.75–8.58	—	—	—	—	—	—
20–24	52	4.16	3.18–5.46	2‖	5.91	0.72–21.50	0.70	0.17–2.89	0.627
25–29	29	4.58	3.19–6.58	6	2.87	1.06–6.29	1.59	0.66–3.84	0.298
30+	17	6.35	3.97–10.17	21	0.59	0.39–0.91	10.77	5.68–20.41	<0.001
Total	731	7.35	6.84–7.90	29	0.76	0.53–1.10	9.64	6.65–13.97	<0.001
b. > 1980	695	7.36	6.83–7.92	3	4.50	0.93–13.16	1.63	0.52–5.07	0.307
b. ≤ 1980	36	4.05	2.92–5.60	26	0.78	0.53–1.14	5.21	3.14–8.62	<0.001



Rimoin AW et al Proc Nat Acad Sci (USA) 2010

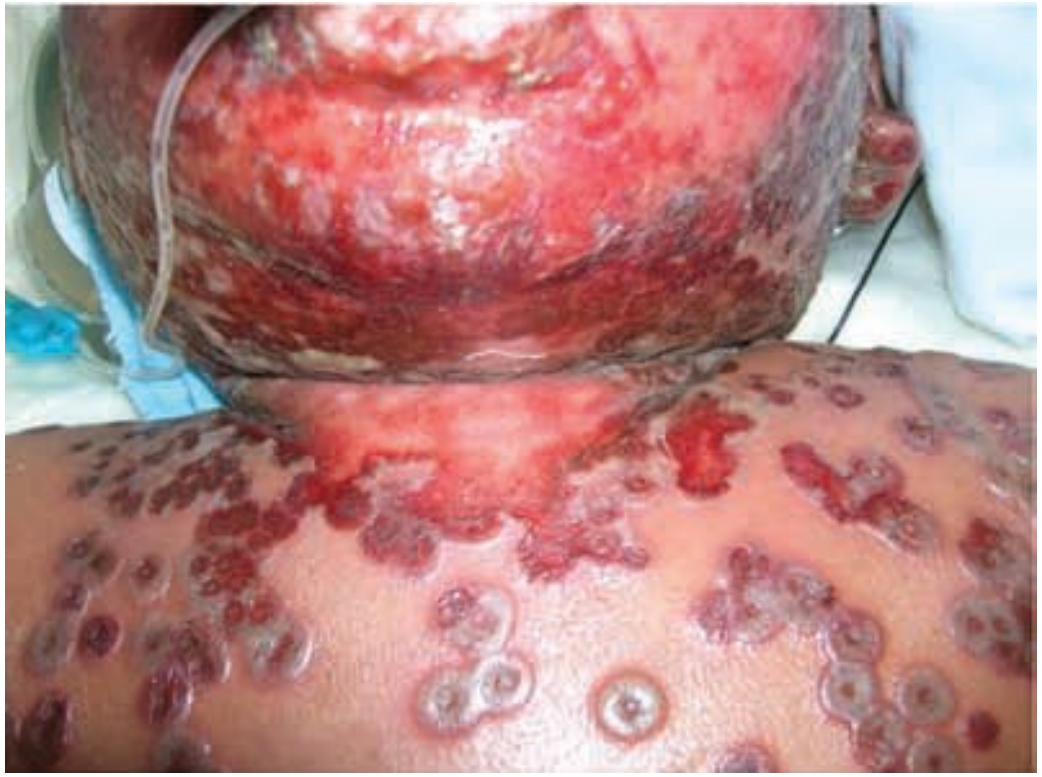
Comparing ACAM2000 and Jynneos vaccines

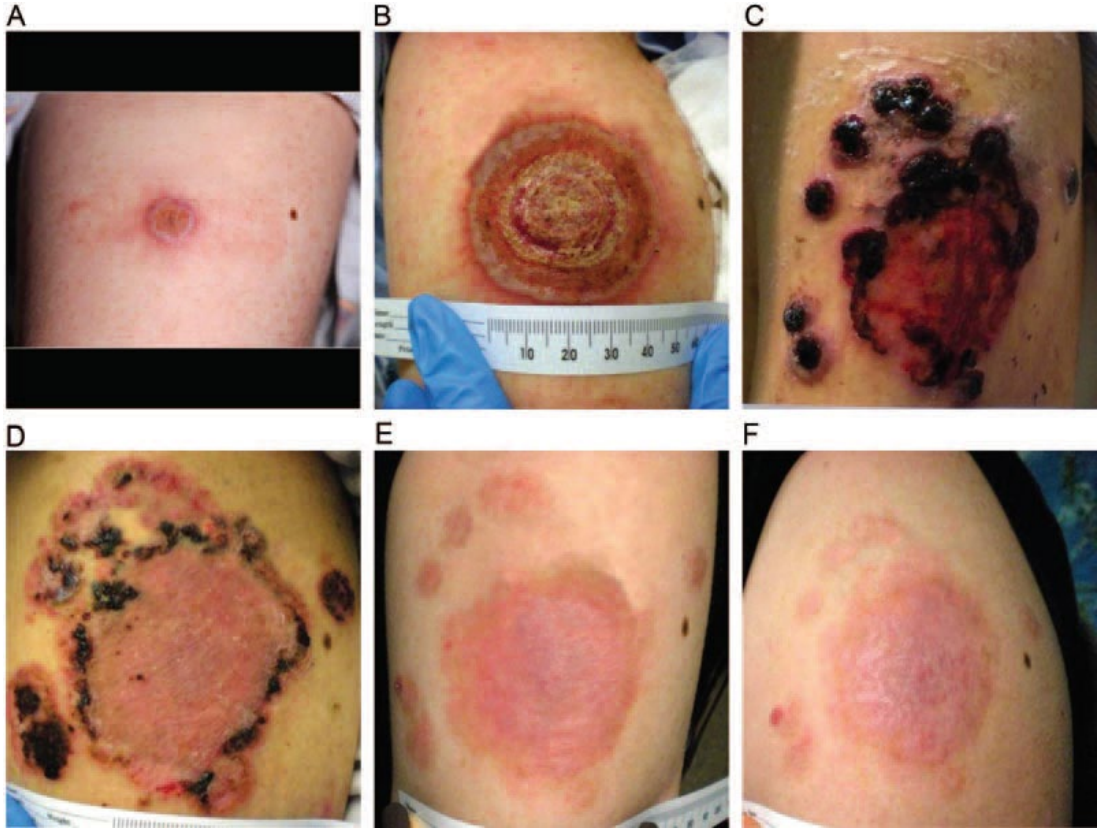
Characteristic	Vaccine product	
	ACAM2000*	JYNNEOS
Vaccine virus	Replication-competent vaccinia virus	Replication-deficient modified vaccinia Ankara
"Take" following vaccination†	Yes	No
Risk for inadvertent inoculation and autoinoculation	Yes	No
Risk for serious adverse event	Yes	No significant events identified during clinical trials
Risk for cardiac adverse events	Myopericarditis in 5.7 per 1,000 primary vaccinees	Clinical trial data limited in evaluating this outcome; however, no significant events in data abstracted from single study arms§
Assessment of effectiveness	FDA assessed by comparing immunologic response and take rates to Dryvax*	FDA assessed by comparing immunologic response to ACAM2000 and animal studies
Administration	Percutaneously using a bifurcated needle by multiple puncture (scarification) technique,¶ single dose	Subcutaneously, 2 doses 28 days apart



Rao AK et al MMWR 2022

Complications of ACAM2000





Vora S et al Clin Infect Dis 2008
Lederman ER et al J Infect Dis 2012

Current US CDC Guidelines for Vaccination

Strategy	Definition	Criteria
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	Any of the following: • 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 and gender diverse people who have sex with men, 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
Pre-Exposure Prophylaxis (PrEP)	Vaccination **before exposure** to monkeypox	• People in certain occupational risk groups*

*People at risk for occupational exposure to orthopoxviruses include research laboratory workers performing diagnostic testing for *Monkeypox virus,* and members of health care worker response teams designated by appropriate public health and antiterror authorities (see ACIP recommendations).

Source: https://www.cdc.gov/poxvirus/monkeypox/interim-considerations/overview.html; Accessed 31 August 2022

Additional CDC Guidance Regarding Vaccination

- **Vaccine should be given within 4 days of exposure to prevent onset of the disease.**
  - If given between 4–14 days after exposure, vaccination may reduce symptoms, but may not prevent disease.
- **CDC is not encouraging mass vaccination for the general public or for all sexually active people.**
- **In some jurisdictions, consideration of monkeypox vaccine PrEP for individuals at increased risk of monkeypox from non-occupational exposure might start to be considered.**
- **To be most effective, monkeypox vaccine PrEP strategies should be part of a larger prevention effort.**

Source: https://www.cdc.gov/poxvirus/monkeypox/interim-considerations/overview.html; Accessed 31 August 2022

Intradermal vaccination

- **Studies show intradermal vaccination with modified vaccinia Ankara (MVA) ACAM3000 resulted in similar immunogenicity at lower doses compared to subcutaneous or intramuscular dosing[1]**
- **Revised Jynneos EUA allows administration of 0.1 mL i.d.**
- **Caveat:**
  - Once entered, vial must be used within 8 hours

Wilck MB et al J Infect Dis 2010