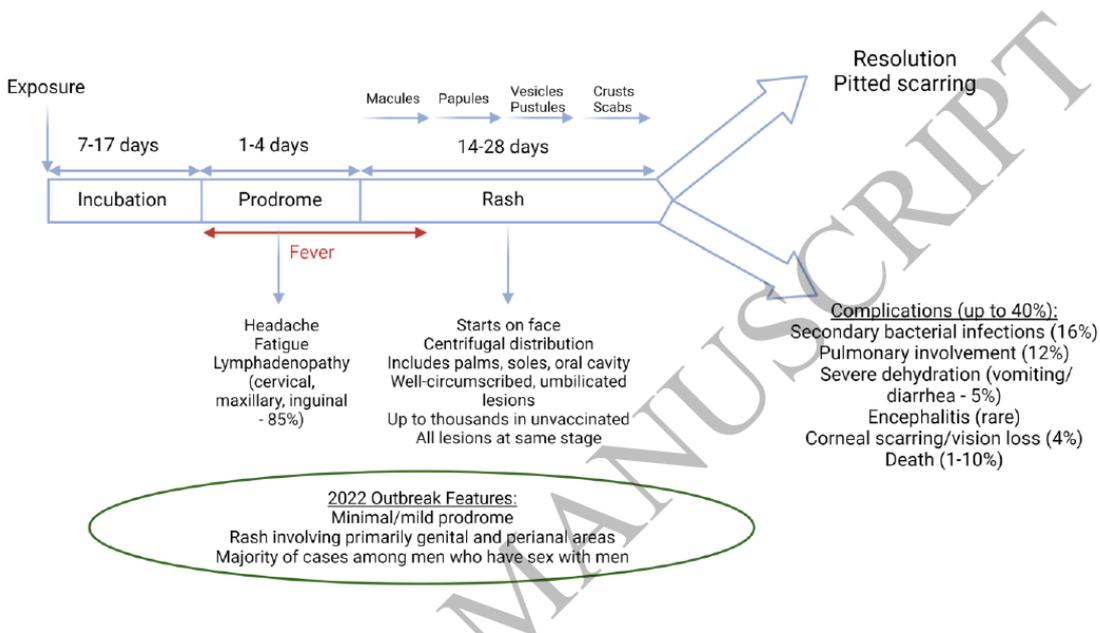


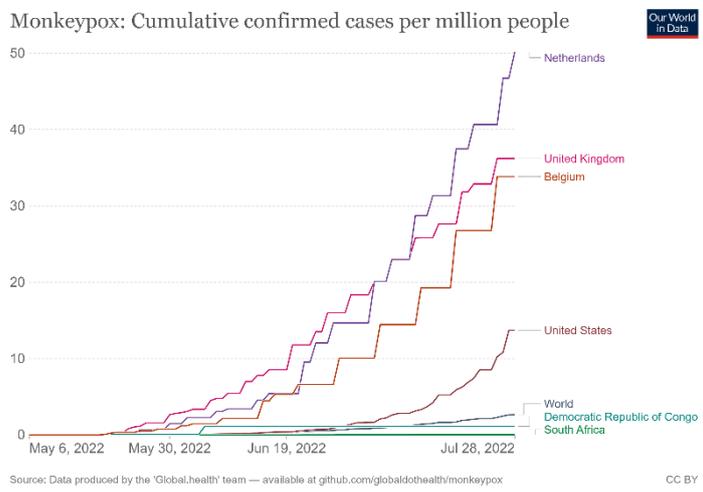
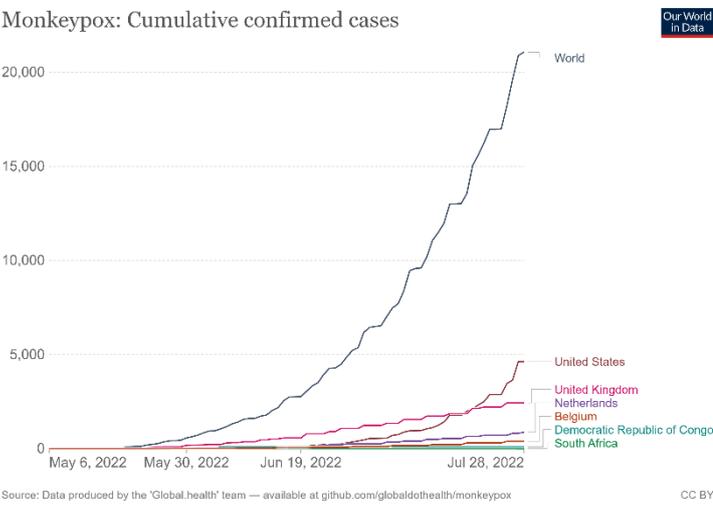
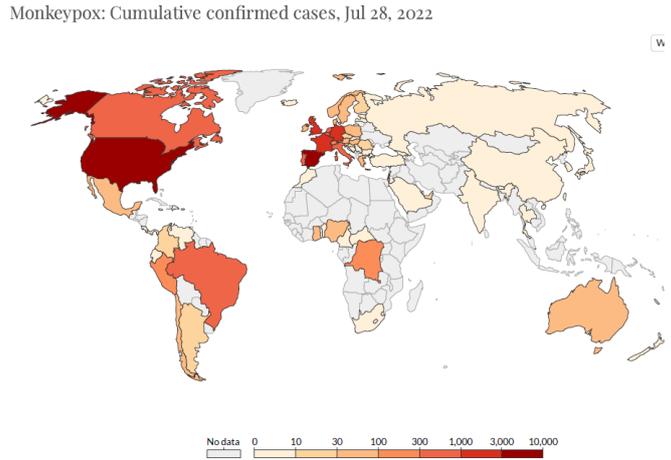
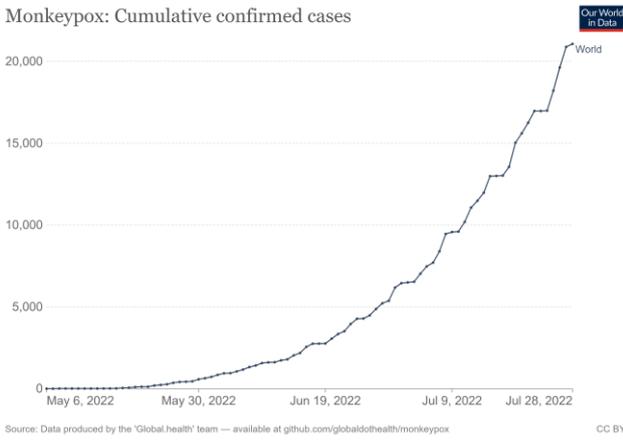
Episode 277: Follow-up on Monkeypox and sudden childhood hepatitis of unknown origin

MONKEYPOX

Clinical course (from Ep 277-5 Fig 2)



Epidemiology (from Our World in Data)



Remark: **confirmed** DRC figures are very low, but according to WHO: *In the Democratic Republic of the Congo, where several thousand cases were suspected, the testing facilities were limited, and support needed to be provided in that regard. The global dashboard did not include suspected cases.*

The first deaths by MPX in Brazil and Spain: <https://www.pbs.org/newshour/health/spain-and-brazil-report-monkeypox-deaths>

Ep 277-1: WHO declares MPX as a PHEIC (public health emergency of international concern), but without internal consensus, because of fear for stigmatization of MSM, who are most affected.

- Fear for an animal reservoir outside Africa
- Until now mostly close contact, maybe sexually transmitted, what about airborne?
- Vaccine inequity: rapid deployment in the North, but NOT in Africa

Ep 277-2: Pediatric cases

A) Tutu Case report from NL Eurosurveillance June 2022:

- An alert 10 yrs old child in overall good health with stable vital parameters and without fever
- Centrifugal distribution of 20 solitary, sharply demarcated, red-brown vesicles; none in the mouth or genital region
- *Not able to identify any possible source of the infection.*
- *Sequencing within the clade 3 lineage B.1, with no direct link to any other strains from the Amsterdam region.*

B) Maddison Muller Bloomberg 29 July

According to WHO: more than 80 kids (= 0.4 % of all cases) across several countries, largely through household contacts.

Comment by Jay Varma (Cornell University NYC)

Once someone has it within a household, it's especially easy for the virus to infect others through sharing clothes or towels, by touching sores or prolonged skin-to-skin contact like hugging.

Kids, constantly interacting at schools and day-care centers, may be especially vulnerable. ;.. some fear that if monkeypox were to start spreading in child-centric settings, it could be hard to contain.

*During a **2003 monkeypox outbreak** in the US, which stemmed from rodents imported from Ghana, pediatric patients were more likely to be hospitalized in an intensive-care unit than adults, according to a study published in the journal *Clinical Infectious Diseases*. Almost a third of the 37 confirmed patients were younger than 18, the study showed.*

Ep 277-3: Evelyn Bunge PLOS Negl Dis Feb 2022: Systematic review on MPX since 70's

- Human monkeypox cases has been rising since the 1970s, most dramatically in the DRC.

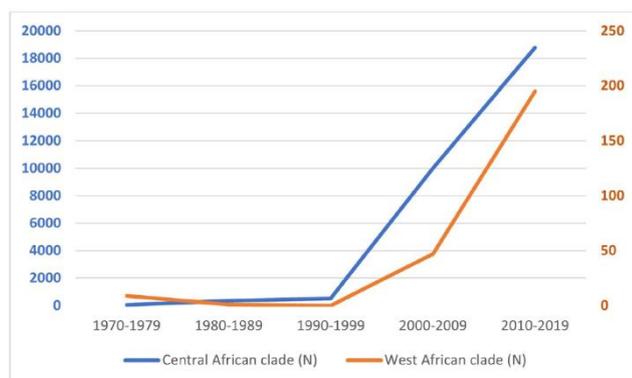


Fig 7. Evolution of number of cases per clade. For 2000–2019, the numbers for the Central African clade are based largely on suspected cases, per the reporting system by the Democratic Republic of the Congo.

<https://doi.org/10.1371/journal.pntd.0010141.g007>

- **The median age at presentation has increased from 4 (1970s) to 21 years (2010–2019).**

- Overall case fatality rate of 8.7%, with a significant difference between clades—Central African 10.6% (vs. West African 3.6% .
- Risk factors for transmission:
 - Human-to-human: sleeping in the same room or bed, living in the same household, or drinking or eating from the same dish
 - Animal-to human:
 - sleeping outside or on the ground or living near or visiting the forest
 - daily exposure to sick animals or cleaning their cages/bedding

Ep 277-4: Wehrle Bulletin WHO **1970**: shows that **airborne transmission of smallpox** occurred in a German hospital from a source case with extensive rash and **cough**, low relative humidity in the hospital and **air currents which caused rapid dissemination of the virus.**

According to recent update of CDC, cough is a possible symptom of MPX: see <https://www.cdc.gov/poxvirus/monkeypox/symptoms.html>

Signs and Symptoms Updated July 29, 2022

- Fever
- Headache
- Muscle aches and backache
- Swollen lymph nodes
- Chills
- Exhaustion
- Respiratory symptoms (e.g. sore throat, nasal congestion, or cough)
- A rash that may be located on or near the genitals (penis, testicles, labia, and vagina) or anus (butthole) but could also be on other areas like the hands, feet, chest, face, or mouth.
 - The rash will go through several stages, including scabs, before healing.
 - The rash can look like pimples or blisters and may be painful or itchy.

You may experience all or only a few symptoms

- Sometimes, people get a rash first, followed by other symptoms. Others only experience a rash.
- Most people with monkeypox will get a rash.
- Some people have developed a rash before (or without) other symptoms.

Monkeypox symptoms usually start within 3 weeks of exposure to the virus. If someone has flu-like symptoms, they will usually develop a rash 1-4 days later.

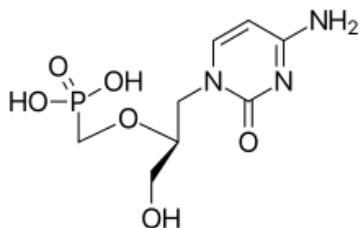
Monkeypox can be spread from the time symptoms start until the rash has healed, all scabs have fallen off, and a fresh layer of skin has formed. The illness typically lasts 2-4 weeks.

If You Have a New or Unexplained Rash or Other Symptoms...

- Avoid close contact, including sex or being intimate with anyone, until you have been checked out by a healthcare provider.
- If you don't have a provider or health insurance, visit a public health clinic near you.
- When you see a healthcare provider, wear a mask, and remind them that this virus is circulating in the area.

Ep 277-5: Emily Siegrist **3 potential drugs for MPX**

- 1) **Cidofovir** (nucleotide analogue CDV), brand name: **Visitide®** = acyclic monophosphate nucleotide analog of [deoxycytidine](#) = POLYMERASE INHIBITOR



- Approved for human CMV retinitis,
- Proven activity against poxviruses:
 - Moluscum contagiosum in humans
 - Vaccinia, cowpox, **monkeypox** and mousepox in animal models, but usually given rather shortly after infection.

Must be given intravenously,

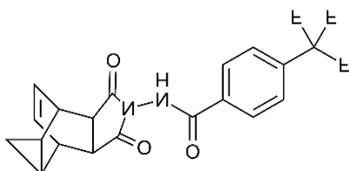
Known pattern of resistance, but inducing lower virulence

Potentially nephrotoxic (dose-dependent)

- 2) **Brin-cidofovir** (BCV)= lipid conjugated cidofovir, brand **Tembexa®**, **orally available and FDA approved for smallpox**

- Lower nephrotoxicity, some GI discomfort.
- Good results in animal models with various poxviruses if given early (max 2-3 days post-infection)
- Human data mainly in CMV and adenoviral prophylaxis in hematogenic stem cell transplantation were variably

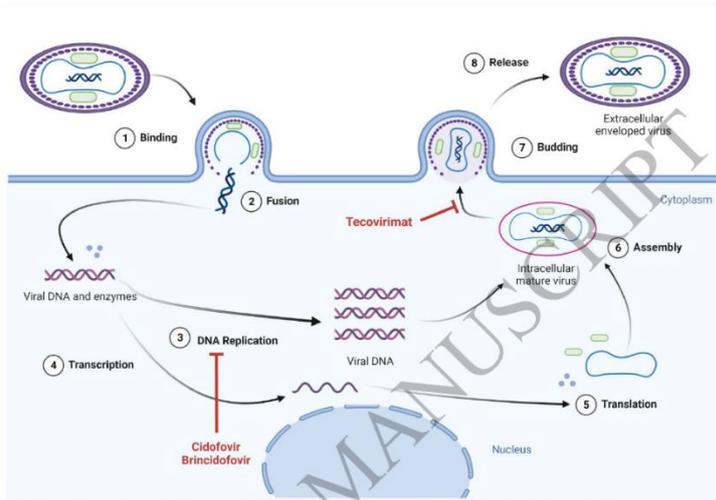
- 3) **Tecovirimat** (ST-246) **TPOXX®** = selective for orthopox,



- it targets membrane protein p37, responsible for formation of enveloped virus, major contributor to cell-to-cell transmission and transmission through the bloodstream to distant tissues.
- does not inhibit the formation of mature virus (MV), which remains in the host cell until cell lysis.

Both oral and IV formulation

- Resistance can be induced, but there is no cross-resistance between CDV or BCV and Tecovirimat; potentially synergistic activity.
- Proven activity in several animal models, but start within 72 hours and minimum duration of 10 days of treatment required.
- Early evidence of activity against MPX in humans; formal trials ongoing.



CONCLUSIONS:

- 1) The epidemic is spreading, still mainly amongst MSM, but **small proportion of women and children**
- 2) In contrast to previous reports from Africa, **very few people die.**
- 3) **Transmission may occur before symptoms are apparent.**
- 4) **Airborne transmission** of smallpox has been described and may be possible with MPX.
- 5) **Tecovirimat** is the most promising drug, but synergism with **(brin)cidofovir** is possible.

Additional info:

<https://www.rivm.nl/en/monkeypox>

<https://www.who.int/news-room/fact-sheets/detail/monkeypox#:~:text=Typically%2C%20up%20to%20a%20tenth%20of%20persons%20ill,infection%20which%20was%20declared%20eradicated%20worldwide%20in%201980.>

MYSTERY of PEDIATRIC HEPATITIS of unknown origin resolved?

Over the last few months about 1000 cases of this uncommon hepatitis have been recorded, with 22 deaths (= 2 % CFR). Curiously, this epidemic seems to calm down spontaneously.

Two small studies from UK (Ep 277-6 A-D) now strongly suggest that a **co-infection of Adeno-Associated Virus-2 (AAV-2) with either Adeno F41 or Human Herpes Virus 6 (HHV-6)** is the culprit, in a particular genetic background: HLA DRB1*04:01.

Remarkably, infection with these viruses is very common and the HLA type is also not uncommon (16%). However, it was shown that during COVID epidemic, infections with Adenoviruses dropped dramatically in children, but rapidly caught up afterwards, which might explain the sudden appearance of this uncommon type of hepatitis (which in normal times presumably was also present at very low frequency, but remained “under the radar”).

Best wishes,

Guido