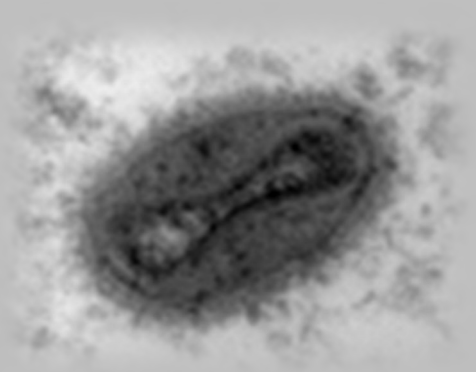
Validation and Performance of an Orthopoxvirus Laboratory Developed Test with Early Detection of Mpox Virus in Residual Lesion Specimens



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Vanderbilt University Medical Center (VUMC)

APHL Lab Con
March 15, 2023

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MEDICAL CENTER

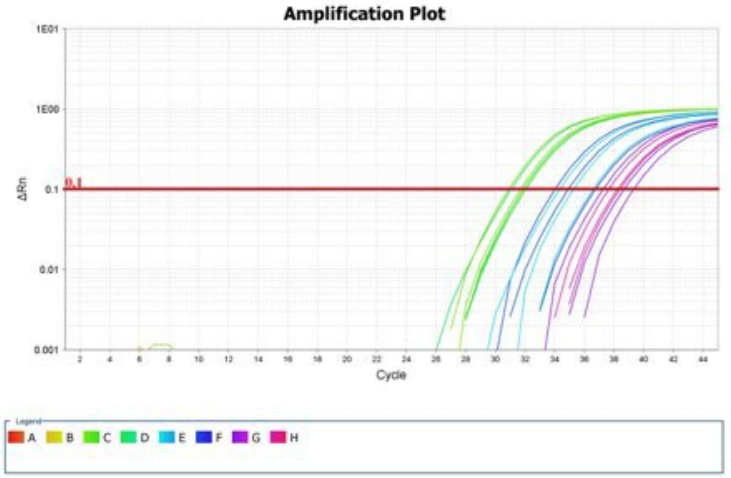
Disclosures (DCG)

- Research funding / Reagents
  - Illumina, Inc.
  - IDbyDNA, Inc.
- Honoraria
  - American Association of Clinical Chemistry
- Consulting
  - BioMerieux, Inc.

Objectives and Overview

- Objectives
  - Understand an academic laboratory approach to a public health threat
  - Appreciate the key partnerships between public health and academic microbiology laboratories
  - Utilize lessons from Mpox to determine best-approach responses to the next global infectious event

- Overview
  - Director perspective
  - Lead technologist perspective



Pox and the Bard of Avon

A pox damn you, you muddy rascal, is that all the comfort you give me?

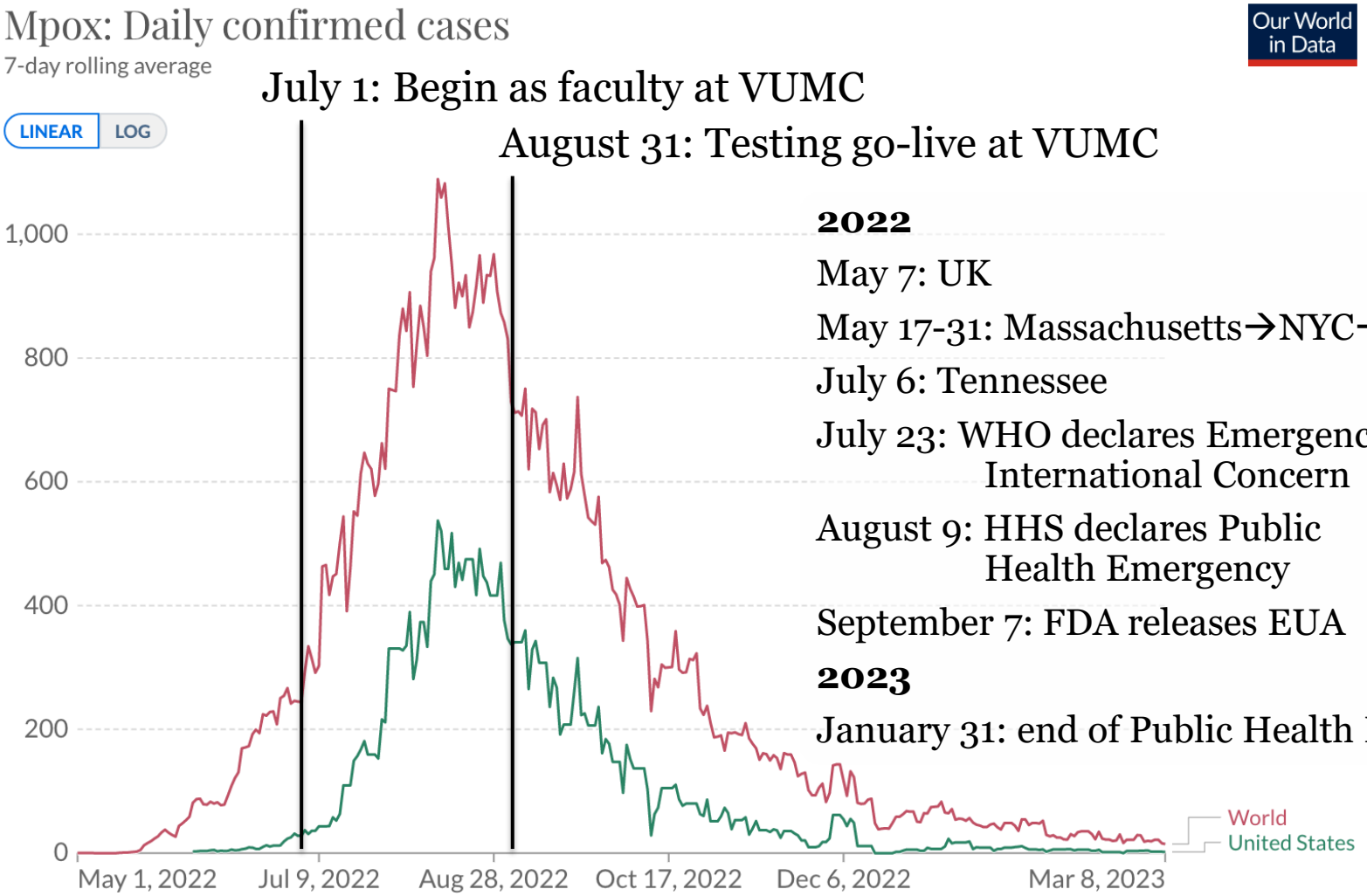
Henry IV

A pox o' your throat, you bawling, blasphemous, incharitable dog!

The Tempest

John Taylor; National Portrait Gallery, London, UK

Mpox: Evidence that I cannot predict the future



2022

May 7: UK

May 17-31: Massachusetts→NYC→Multiple

July 6: Tennessee

July 23: WHO declares Emergency of International Concern

August 9: HHS declares Public Health Emergency

September 7: FDA releases EUA

2023

January 31: end of Public Health Emergency

https://ourworldindata.org/monkeypox (Accessed 3/8/23)

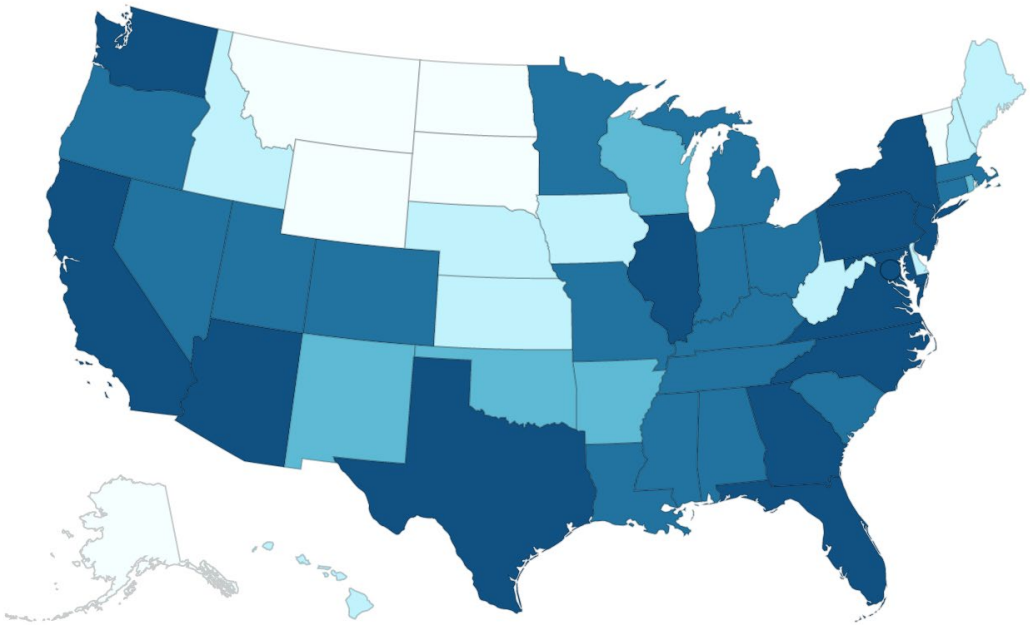
2022 U.S. Map and Case Count

U.S. Cases

Total Cases
30,225

U.S. Deaths

Total Deaths
38



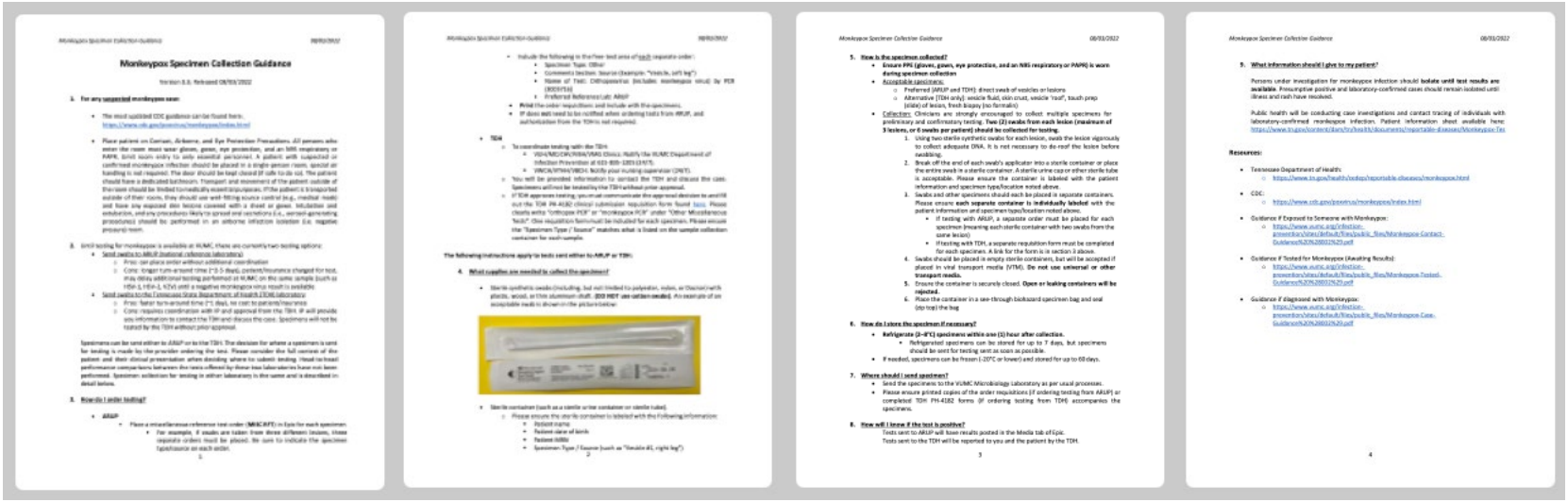
TN: 396

https://www.cdc.gov/poxvirus/monkeypox/response/2022/us-map.html Updated 3/8/22

Key Issues at the Beginning …

- Bring testing in-house, or send it out?

- How to best communicate complex ordering requirements?



Key Issues at the Beginning …

- How do we ensure safety?
  - Patients and Clinical Staff
  - Laboratory staff

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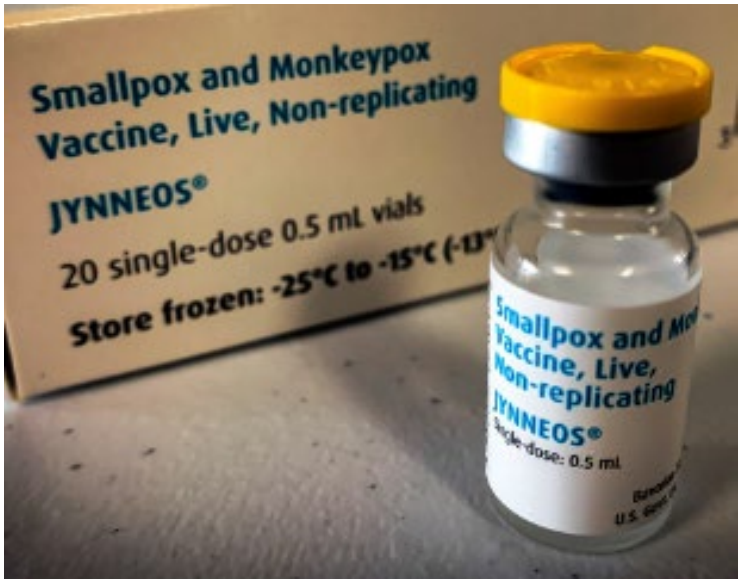
Department of Infection Prevention



Key Validation Questions

- Select agent?
- Specimen sources?
- Swab types?
- Transport media?
- Inactivation?
- Turn-around time?
- Acceptable limit of detection?
- Biohazard waste?
- EUA?
- Validation materials?
- Reporting?
- Reimbursement?
- Reagent availability?

What approach will best serve our patients?

FDA-IVD Approved, CDC Developed Assay

CDC	Centers for Disease Control & Prevention Poxvirus & Rabies Branch (PRB)		
Test Procedure: *Monkeypox virus* Generic Real-Time PCR Test			
Rev. No. 01	**Issued Date:** 6/6/2022		**Page** 1 of 7

Target: MPXV Extracellular enveloped virus protein gene B6R

CDC	Centers for Disease Control & Prevention Poxvirus & Rabies Branch (PRB)		
Test Procedure: Non-variola Orthopoxvirus Generic Real-Time PCR Test			
Rev. No. 02	**Issued Date:** 6/6/2022		**Page** 1 of 8

Target: Orthopoxvirus DNA polymerase gene E9L

Li Y. J Clin Virol. 2006 Jul;36(3):194-203. PMID: 16731033

Considerations for an LDT: Speed, Reliability, Safety

- **Platform Selection** – bioMerieux EMAG, QuantStudio7

- **Assay Selection** – RealStar Zoonotic Orthopoxvirus PCR Kit (Altona Diagnostics)
  - Developed in collaboration with CDC (2006)
  - Available as RUO
  - Scalable
  - Includes:
    - Positive PCR control (cowpox virus)
    - Internal extraction/PCR control
  - Target: Non-Variola Orthopoxvirus

- **Safety Measures** –

  Virus inactivation steps

UK Health Security Agency

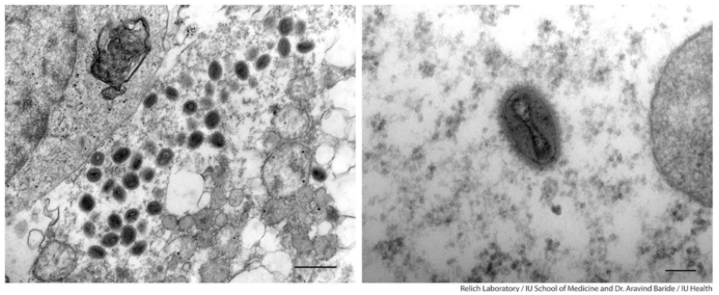
Monkeypox Virus Inactivation Testing Report

Report identifier	HCM/MPx/007/v1
Report date	23 June 2022
Testing laboratory	High Containment Microbiology, UK Health Security Agency (UKHSA)

Validation Material Selection

- **Positive Qualitative Material:** Vaccinia Virus (ATCC)

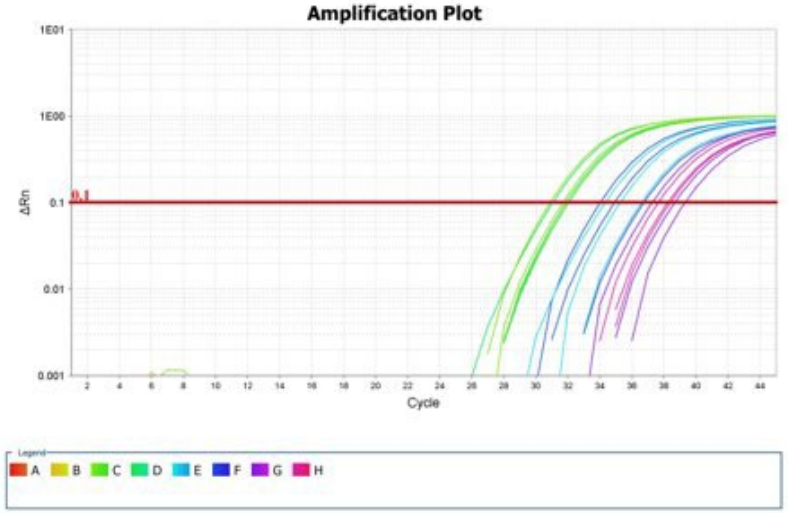
- **Positive Quantitative Material**
  - University of Indiana Clinical Microbiology colleagues
  - Culture clinical Mpox specimens
  - Harvest, Extract, Quantitate DNA
  - 3 individual viral preparations
  - Confirmed non-infectious



- **Negative Matrix:** Residual patient samples: lesions tested for HSV and VZV prior to Mpox emergence

Validation Plan

- **Accuracy:** 37 positive contrived vaccinia virus (ATCC), 1 Mpox positive co-tested at TDH, 30 negative (100%)
- **Repro/Precision:** 7 operators, 10 days, multiple reagent lots (96%)
- **LoD:**
  - Quantitated Mpox (3) extracted and assayed in serial dilution
  - 1x10^3 genomic copies/mL
  - Ct 37-39
- **Analysis:**
  - Ct cutoff for positivity 40.0
  - All results reviewed for clinical correlation if Ct > 37, per CDC Guidelines



Validation Plan

- **Specificity:** HSV-1, HSV-2, and VZV - no cross-reactivity
- **Inhibitory Substances:** Vaccinia Virus (high and low titer)
  - Blood, Urine, Feces, Antibiotic Ointment, Hydrocortisone
  - Feces and 10% blood showed inhibition (target and internal control)
- **Stability:** Mpox near LoD, stable over 72 hours, 4 degrees and RT

Workflow

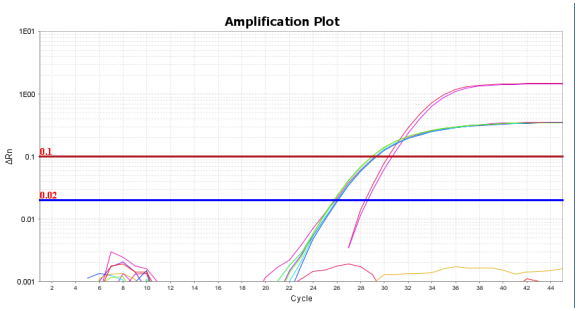
Inactivation

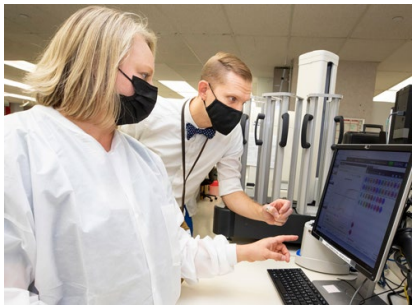
Extraction

Manual Assay Setup

Real-Time PCR

Manual Data Analysis





Safety and Stewardship

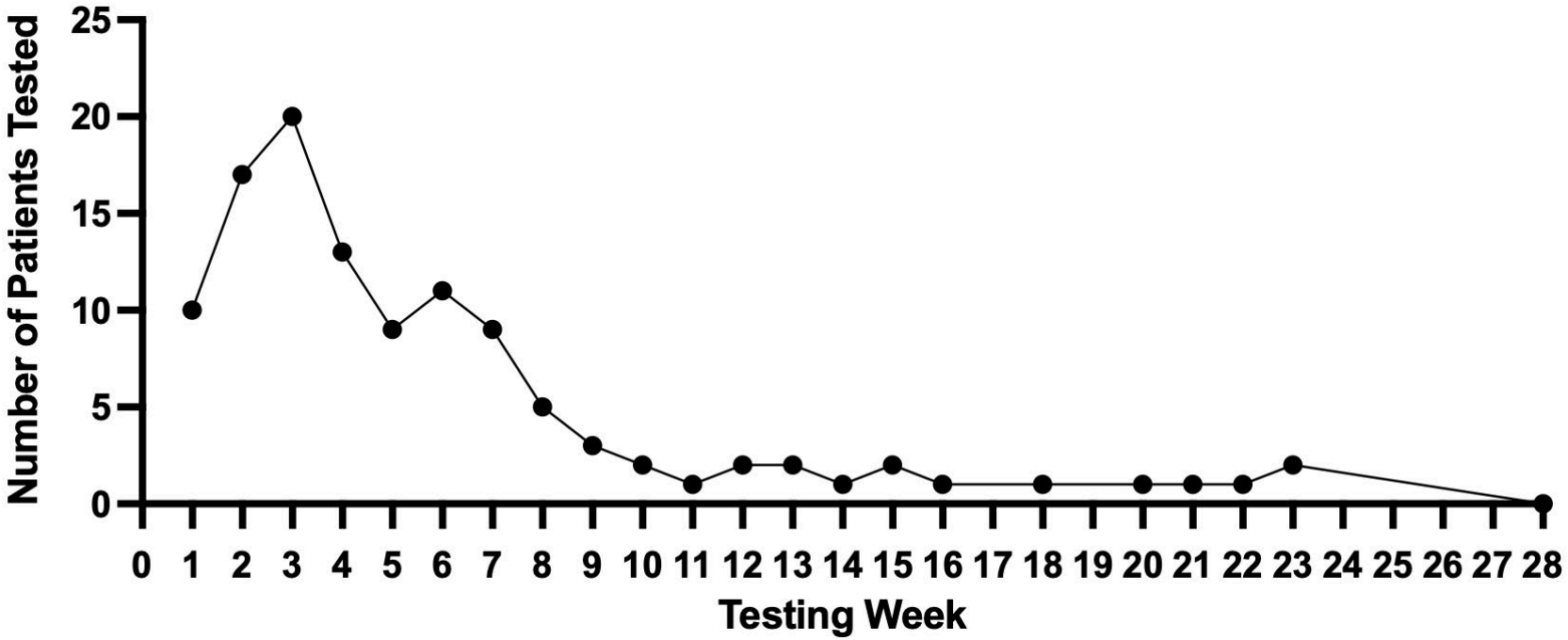
- **Safety**
  - TDH/CDC coordinated vaccination of all testing personnel
  - Senior, experienced MLS chosen
  - Dedicated lab space for virus inactivation
  - HSV and VZV lesion co-testing testing sequestered

- **Ordering restrictions**
  - Initial testing sent to TDH was coordinated through infection control
  - LDT had no ordering restrictions, stewardship managed through individual physicians
- **Public Health:** Infection Control and laboratory coordinated sending positive results to TDH

Monkeypox Virus Detection at VUMC

Total number of patients tested: 114
Mpox diagnosis: 30

Overall 26.3% positivity

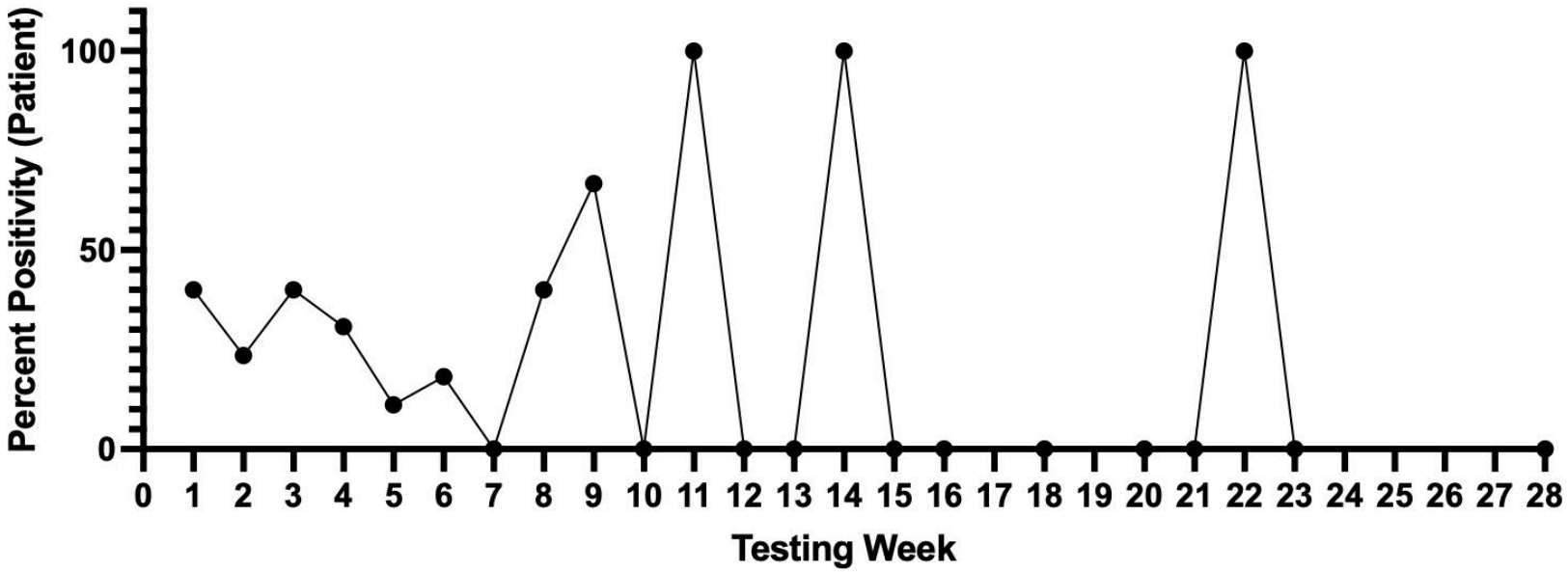


Date range: 9/1/22 – 3/8/22

Monkeypox Virus Detection at VUMC

Total number of patients tested: 114
Mpox diagnosis: 30

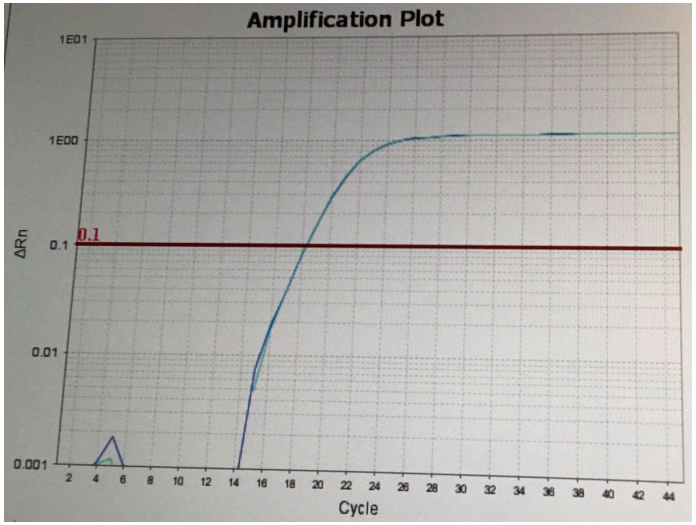
Overall 26.3% positivity

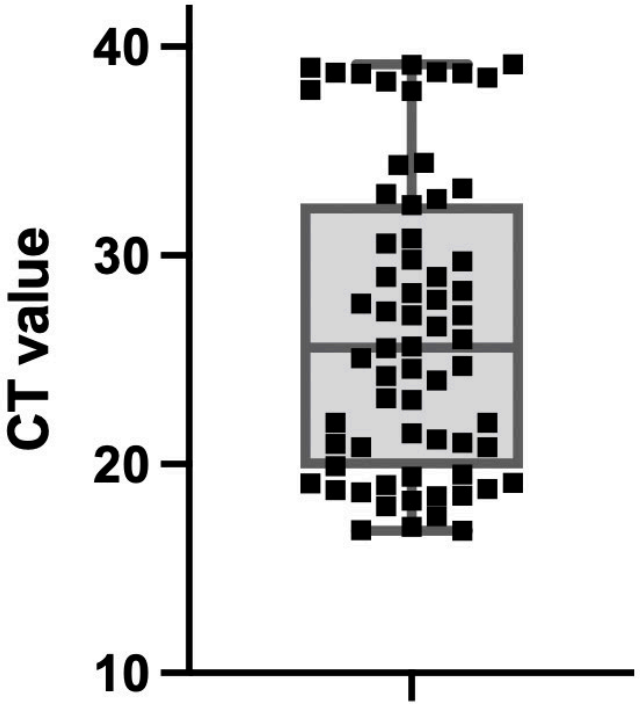


Date range: 9/1/22 – 3/8/22

Monkeypox Virus Detection at VUMC

First run: 9/1/2022
Positive oral lesion
CT 18.2





39.2 - Max

32.5 – 75%

25.6 - Med

19.8 – 25%

16.8 - Min

Average: 26.6 ± 7.2

Date range: 9/1/22 – 3/8/23

Retrospective Review

- Was Mpox present in Tennessee prior to declared public health emergency in central TN?
- 101 residual lesion specimens (pools) submitted for HSV-1/2 and/or VZV testing
- One pool was positive – separate specimen from a patient in this pool was confirmed to contain Mpox by the TDH
- Detection of Mpox in this specimen is consistent with the known timing of Mpox arrival in central Tennessee.
- This specimen was handled for other testing – unintentional workplace Mpox exposure?
- Precautions are necessary to protect laboratory professionals
  - Sequester co-testing samples
  - Dedicated team for HSV and VZV lesion testing
  - Class II Biosafety hood requirement

Lessons Learned, and Preparing for the next Infectious Event …

FDA Mpox Virus Emergency Use Authorization (EUA)

Contains Nonbinding Recommendations

Policy for Monkeypox Tests To Address the Public Health Emergency

Guidance for Laboratories, Commercial Manufacturers, and Food and Drug Administration Staff

Document issued on the web on September 7, 2022.

For questions about this document, contact MPXDx@fda.hhs.gov.

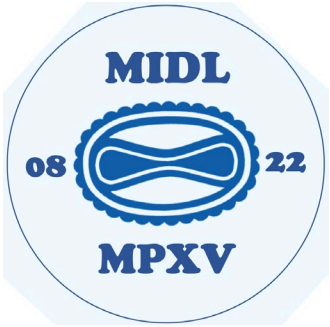
FDA U.S. FOOD & DRUG ADMINISTRATION
CENTER FOR DEVICES & RADIOLOGICAL HEALTH

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Devices and Radiological Health

https://www.fda.gov/regulatory-information/search-fda-guidance-documents/policy-monkeypox-tests-address-public-health-emergency?utm_medium=email&utm_source=govdelivery

Mpox Virus Whole Genome Sequencing (WGS)

VUMC PMI



VANTAGE: VANDERBILT TECHNOLOGIES FOR ADVANCED GENOMICS

Operationalized NGS is Needed Now, and is Future Facing

Steffano Bertuzzi, PhD
ASM CEO

THE HILL

What world leaders must understand about microbes in a global pandemic

BY STEFANO BERTUZZI, PH.D, MPH, OPINION CONTRIBUTOR — 10/05/21 06:30 PM EDT
THE VIEWS EXPRESSED BY CONTRIBUTORS ARE THEIR OWN AND NOT THE VIEW OF THE HILL

161 COMMENTS

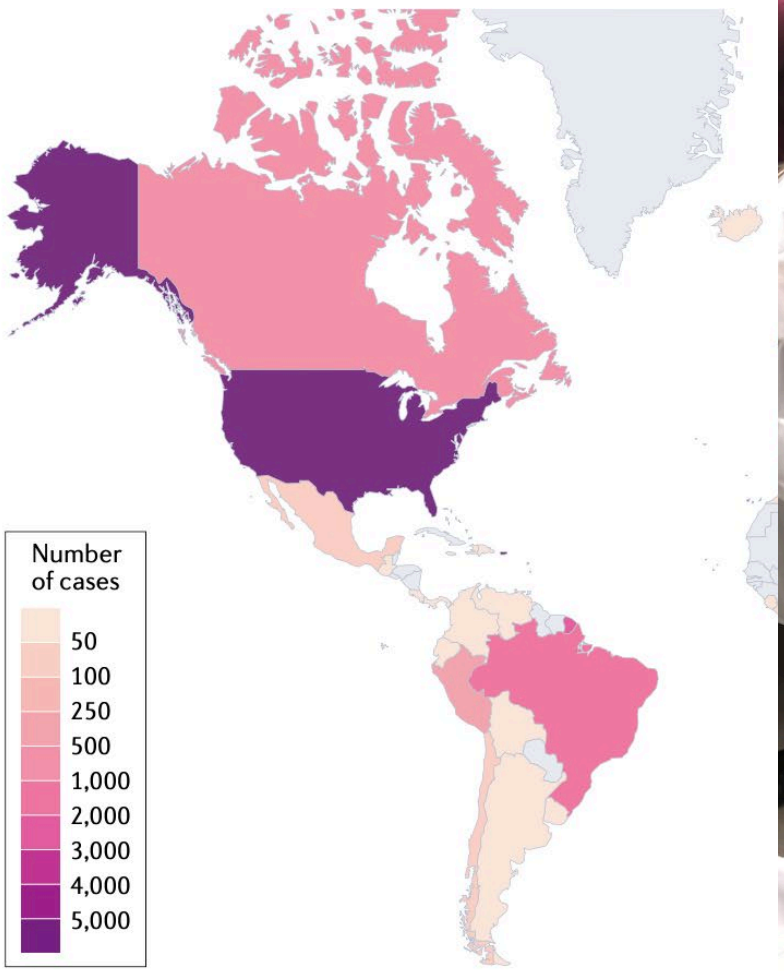
"We have a **momentous opportunity** before us now at the U.S. Centers for Disease Control and Prevention (CDC). The CDC has significantly increased its **Advanced Molecular Detection (AMD) program**, a result of an unprecedented funding of over $1.75 billion. I applaud such visionary efforts and think the program will be executed effectively by **ramping up the sequencing of SARS-CoV-2 variants and other pathogens through the power of "next-generation sequencing."** These new genetic technologies can rapidly identify novel viral strains, providing invaluable information for research, surveillance, and patient treatment.

However, if advanced programs such as AMD in the U.S. and programs in other "developed" countries remain national boutiques, they will not achieve the tremendous potential they can under global governance by experienced leaders. **We do not know where variants will emerge, but we should know the dangers of searching only under lamp posts while ignoring the real dangers in the dark.**

To monitor the microbial world, we need to look far beyond an incomplete circle of well-lit national sampling programs and limited international partnerships. What we need in place to continue fighting this pandemic and to be better prepared for the next is **a global network of pathogen sequencing surveillance and diagnostic infrastructure**."

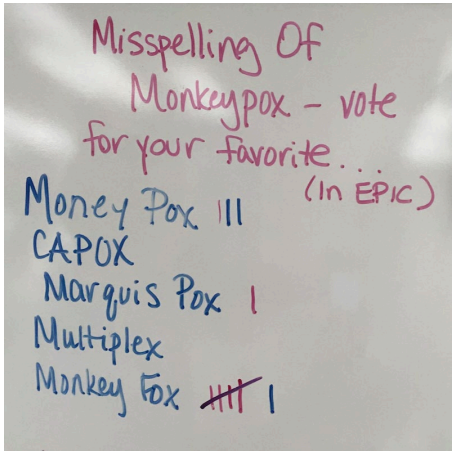
https://thehill.com/opinion/healthcare/575452-what-world-leaders-must-understand-about-microbes-in-a-global-pandemic

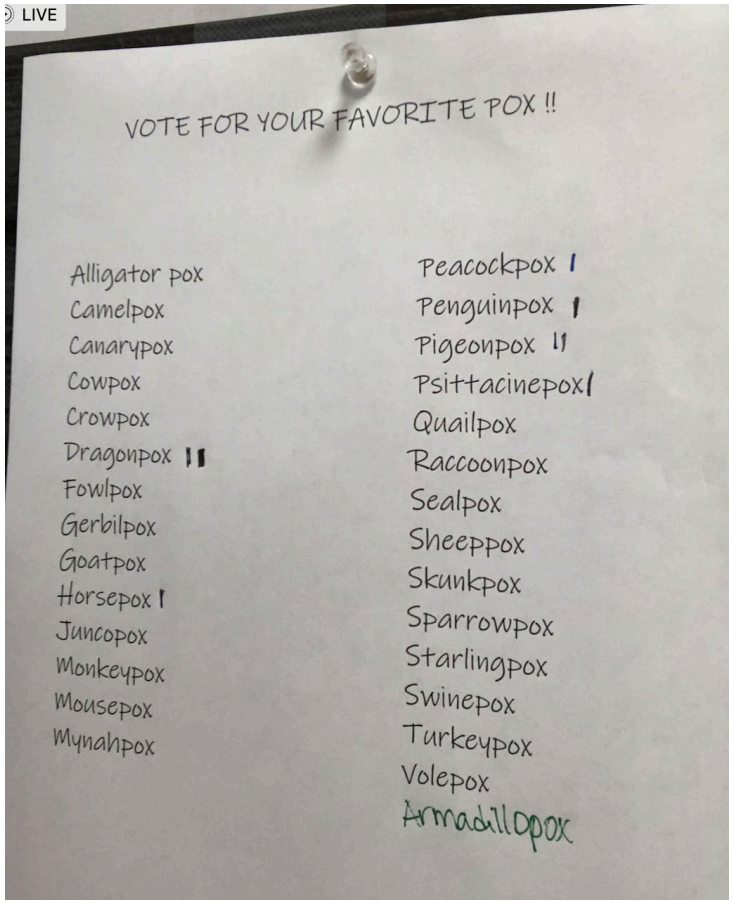
What comes next?



Not Mpox …

https://harrypotter.fandom.com/wiki/Dragon_Pox





https://www.carteblanchehobbies.com/catalog/world_of_warcraft_tcg-betrayal_of_the_guardian/soul_pox/97750

Acknowledgements

MIDL … Everyone!
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Tom Talbot, MD
Mary DeVault
Infection Prevention Team

Lori Rolando, MD
Occupational Health Team

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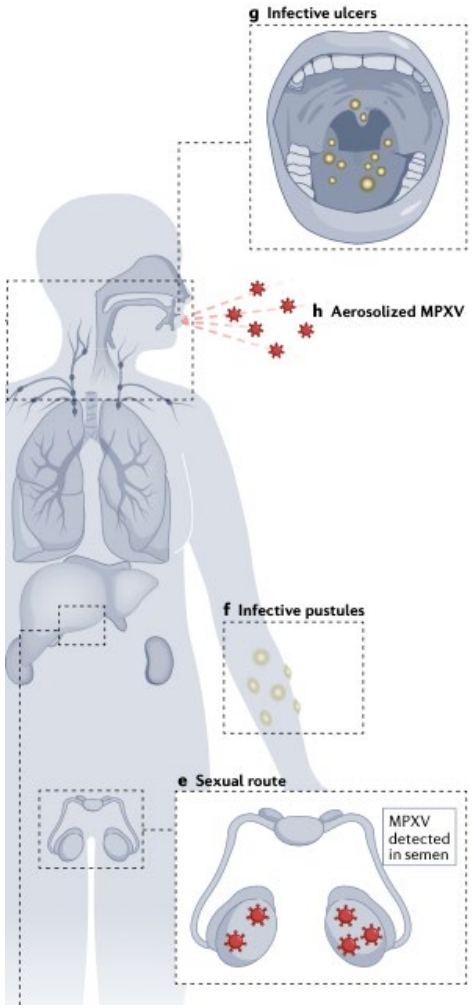
Mpox Virus Basic Virology

- Two strains/clades, Historic regions of endemicity
  - Clade I: ~10.6% mortality
    - Tier 1 select agent
    - DRC, South Sudan
  - Clade II: ~3.6% mortality
    - Current outbreak is lineage B.1
    - Nigeria and surrounding countries
- Zoonotic pathogen
  - Unknown animal reservoir; rodents suspected
- Transmission
  - Direct contact with infected carriers
    - Transmission in historic endemic range
    - 2003 US outbreak – prairie dogs
  - Skin-to-skin contact
  - Aerosolization of large droplets
  - Fomites?

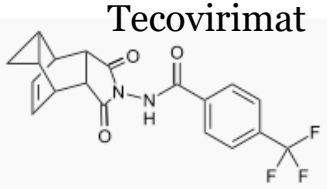


Lum FM. Nat Rev Immunol. 2022 Sep 5. PMID: 36064780

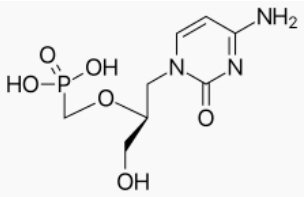
Safety: Treatment and Vaccination

- **Treatment**
  - Tecovirimat (Tpoxx), oral or IV; only available from CDC
    - Targets Orthopoxvirus VP37 envelope wrapping protein
  - Cidofovir, IV
    - Targets viral DNA polymerase
  - Vaccinia immune globulin, IV

Tecovirimat



Cidofovir

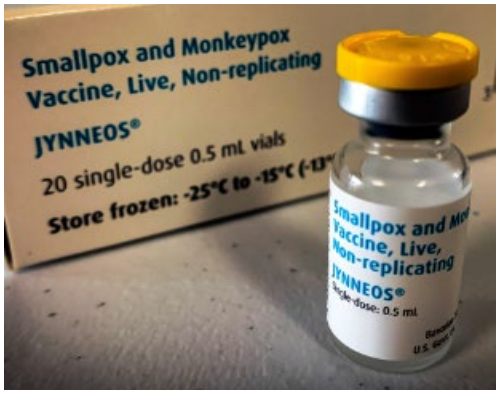


- **Vaccination**
  - Pre-Exposure vs Post-Exposure
    - Vaccine equity / availability
  - Vaccinia (Ankara) derived vaccines
    - ACAM2000 – replication competent
    - JYNNEOS – replication incompetent
  - Dosing based on prior vaccination
  - Waning immunity
  - Serology is not widely available

ACAM2000

vs

JYNNEOS



Pending Challenges with Detection

Audience: Clinical Laboratories
Level: Laboratory Alert

September 2, 2022

CDC is aware of three *Monkeypox virus* (MPXV) cases in California in which preliminary data show a significant deletion in the tumor necrosis factor (TNF) receptor gene. This gene is the target for the CDC West African MPXV and Generic MPXV real-time PCR tests. At this point, the TNF receptor gene deletion is rare. Molecular laboratory developed tests (LDTs) designed using the CDC published primers and probes that specifically target *Monkeypox virus* did **NOT** detect the virus because of the TNF receptor gene deletion in these specimens. These cases were still correctly diagnosed because they were also tested with an LDT that was developed based on CDC's published non-variola *Orthopoxvirus* (NVO) test.

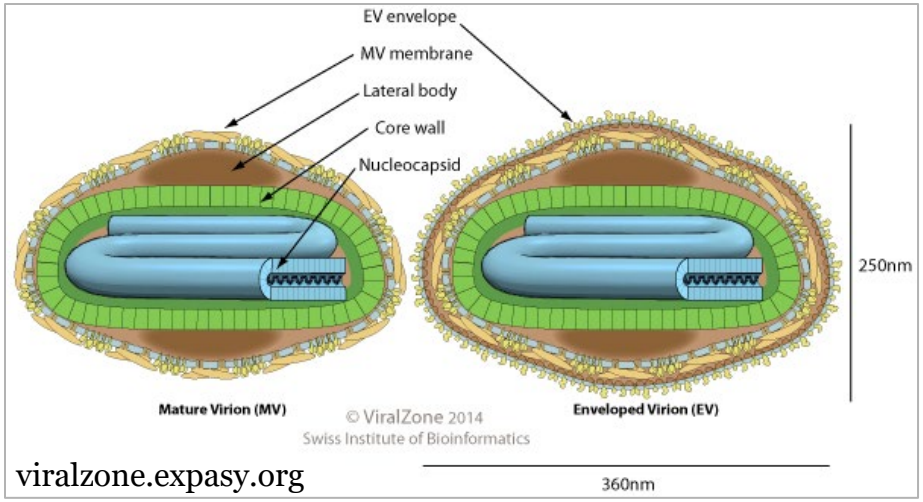
To prevent false negative results:

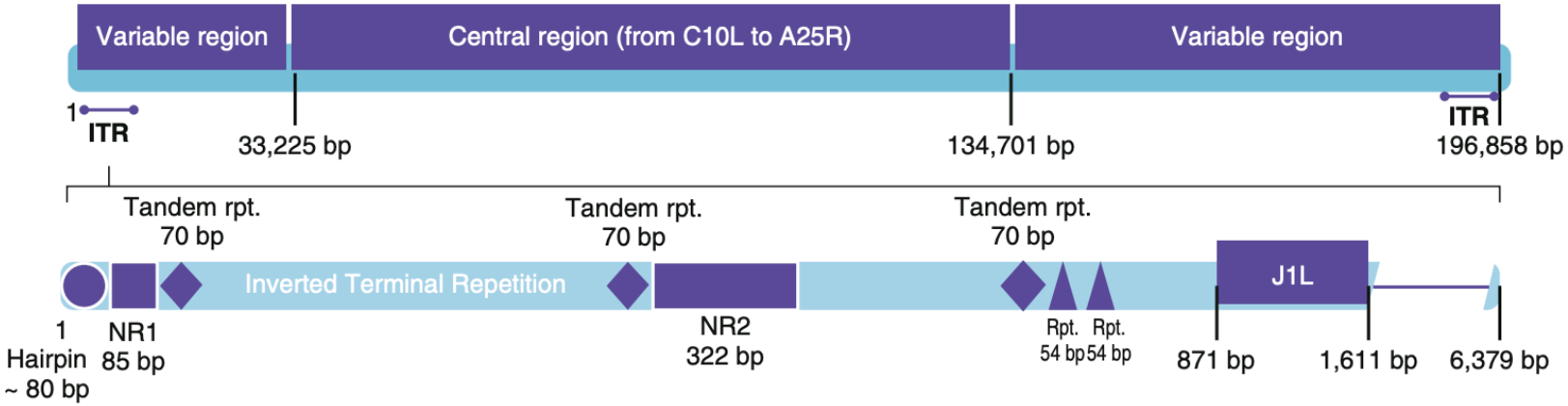
- If your laboratory is using a MPXV-specific LDT, refer highly suspicious *Monkeypox virus* specimens that result as negative to your public health laboratory, or to CDC, to confirm results. Public health laboratories and select commercial laboratories use the CDC FDA cleared NVO test, which can correctly identify *Orthopoxvirus* when the TNF gene deletion occurs.
- Use a multiplex assay that targets multiple viral genes, **or** an assay that targets an essential viral gene which is unlikely to mutate, **or** an assay that detects non-variola *Orthopoxvirus*.

CDC will update the published primer and probe sequence information to alert test developers of this TNF receptor gene deletion.

Monkeypox Virus Basic Virology

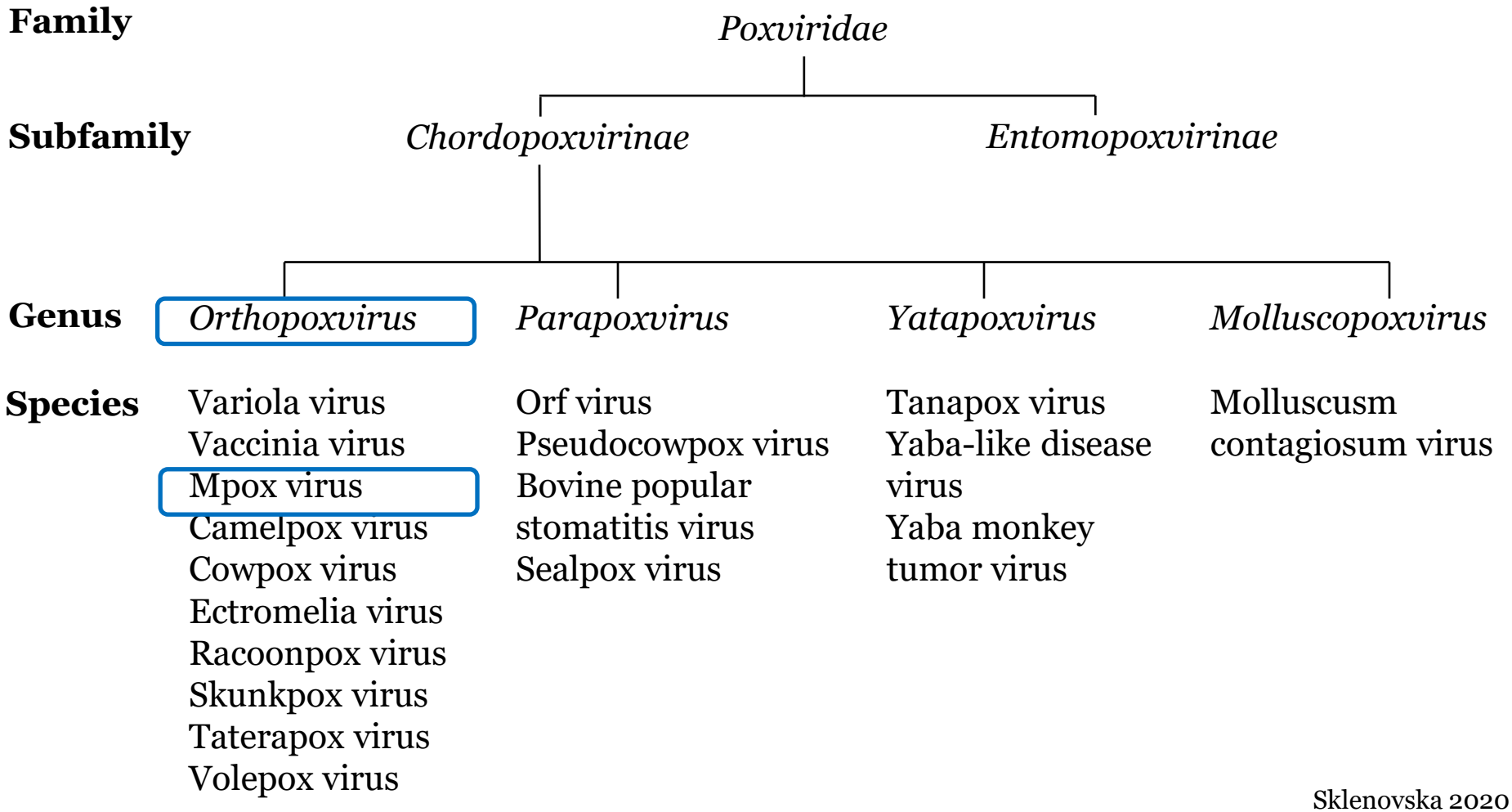
- Large and complex virus
  - Double-stranded DNA virus; Genome ~200kb
  - Dumbbell-shaped core
  - Complex series of membranes composing envelope





Sklenovska 2020

Poxvirus Taxonomy



Sklenovska 2020
Carroll. MCM 12th Ed, 2019

Lesions

Stage	Stage Duration	Characteristics
Enanthem		• Sometimes, lesions first form on the tongue and in the mouth.
Macules	1–2 days	• Macular lesions appear.
Papules	1–2 days	• Lesions typically progress from macular (flat) to papular (raised).
Vesicles	1–2 days	• Lesions then typically become vesicular (raised and filled with clear fluid).
Pustules	5–7 days	• Lesions then typically become pustular (filled with opaque fluid) – sharply raised, usually round, and firm to the touch (deep seated). • Finally, lesions typically 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.



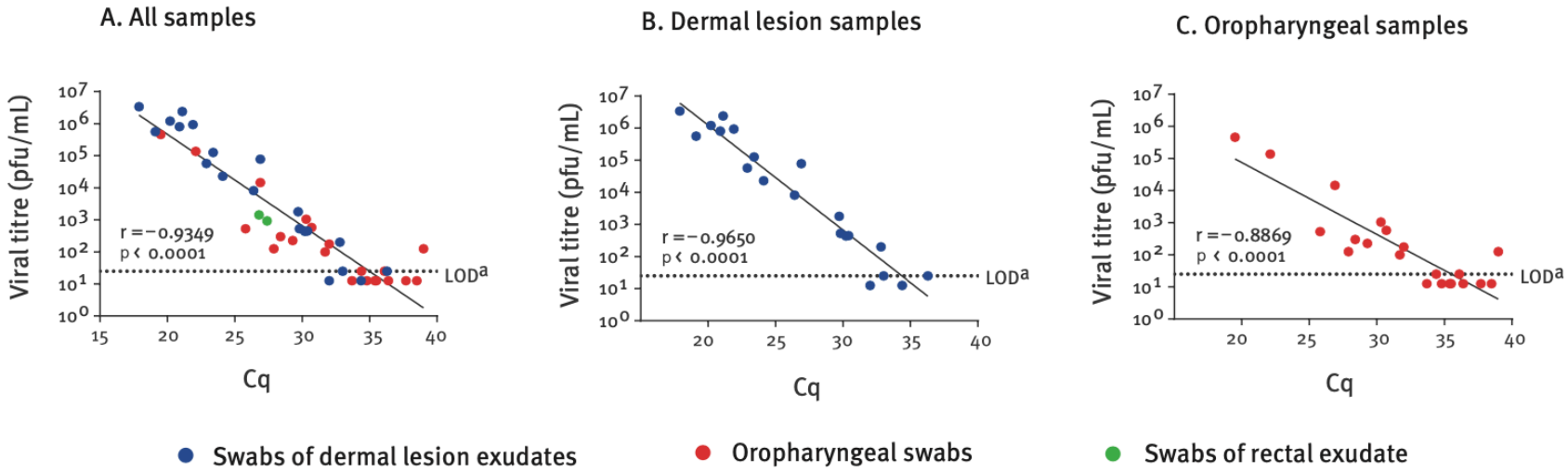




https://www.cdc.gov/poxvirus/monkeypox/clinicians/clinical-recognition.html

CT values and Viral Titers Correlate Well

Correlation between quantity of viral DNA and infectious virus titre in clinical specimens of MPXV infected patients, Israel, 2022 (n = 43 specimens)



Cq: quantitation cycle; LOD: limit of detection (25 pfu/mL); MPXV: monkeypox virus; pfu: plaque forming units.

[a] LOD = 25 pfu/mL.

Forty-three clinical samples (21 oropharyngeal swabs, 20 dermal lesion exudate swabs and two rectal swabs) from 32 patients were each subjected to MPXV-DNA quantification by real-time PCR and infectious-viral-titre determination by plaque assay. PCR results (Cq values), and corresponding infectious virus titres (pfu/mL) are plotted, with samples having a titre below LOD being assigned a value of half the LOD (12.5 pfu/mL). Plots for (A) all samples, (B) dermal lesion exudate samples only, and (C) oropharyngeal samples only are respectively presented with the Pearson correlation coefficient obtained.

Paran N. Euro Surveill. 2022 Sep;27(35). PMID: 36052723

MPXV DNA Persists in Different Anatomic Sites

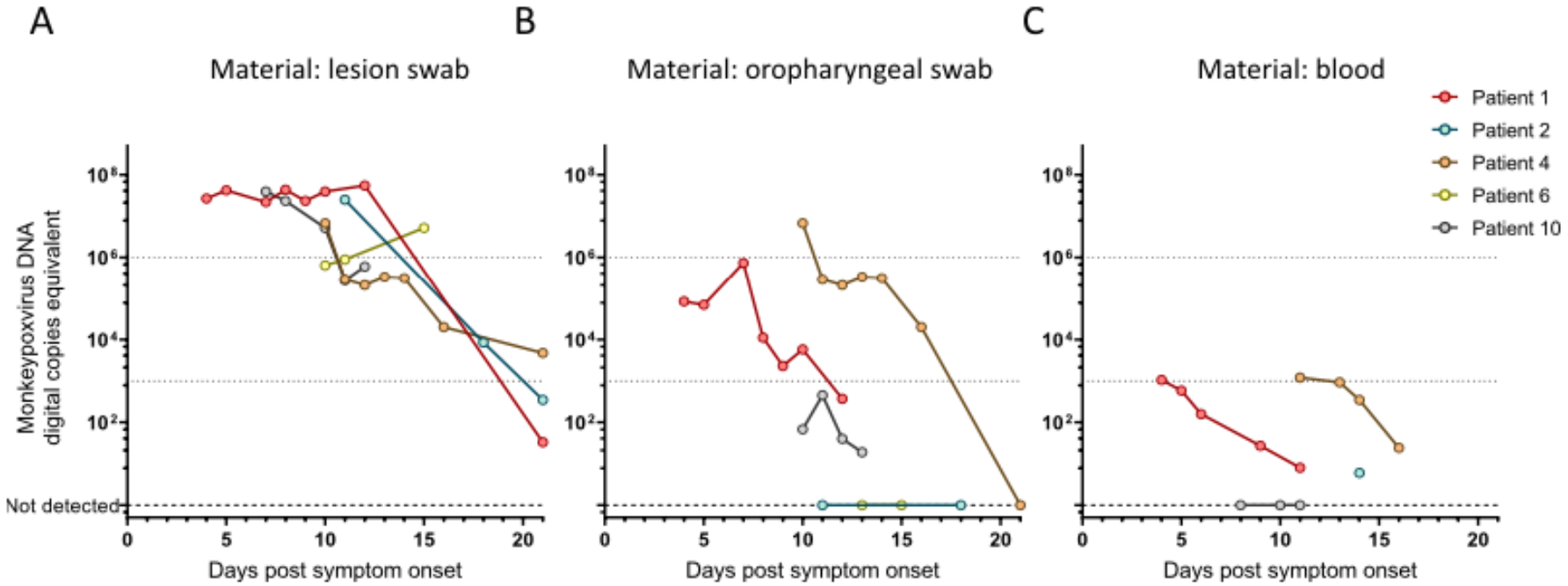


Fig. 1. Viral DNA-load time courses were plotted for hospitalized patients with available serial measurements. A) Swabs from cutaneous lesions were taken according to established procedures; however, the exact location where swabs were taken has not been recorded. Also, swabbing procedures may entail opening a fresh lesion, which will then crust over. The indicated viral loads represent generic lesion swabs from the respective patient, not necessarily from the same lesion. (1st week: median 3.31E+07 cp/ml, range 2.19E+07 – 3.95E+07 cp/ml; 2nd week: median 3.04E+06 cp/ml, range 2.11E+05 – 5.48E+05 cp/ml). Graphs B) and C) represent oropharyngeal swabs (1st week: median 8.44E+04 cp/ml, range 6.93E+04 – 7.31E+05 cp/ml; 2nd week: median 4.04E+03 cp/ml, range 0 – 6.75E+06 cp/ml; 3rd week: median 0 cp/ml, range 0 – 2.00E+04 cp/ml) and EDTA plasma-samples (1st week: median 5.85E+02 cp/ml, range 1.58E+02 – 1.05E+03 cp/ml; 2nd week: median 7.80E+00 cp/ml, range 0 – 1.20E+03 cp/ml; 3rd week: single sample, 2.37E+01 cp/ml) respectively.

Nörz D. J Clin Virol. 2022 Oct;155:105254. PMID: 36057206

Lesions Contain the Most Viral DNA

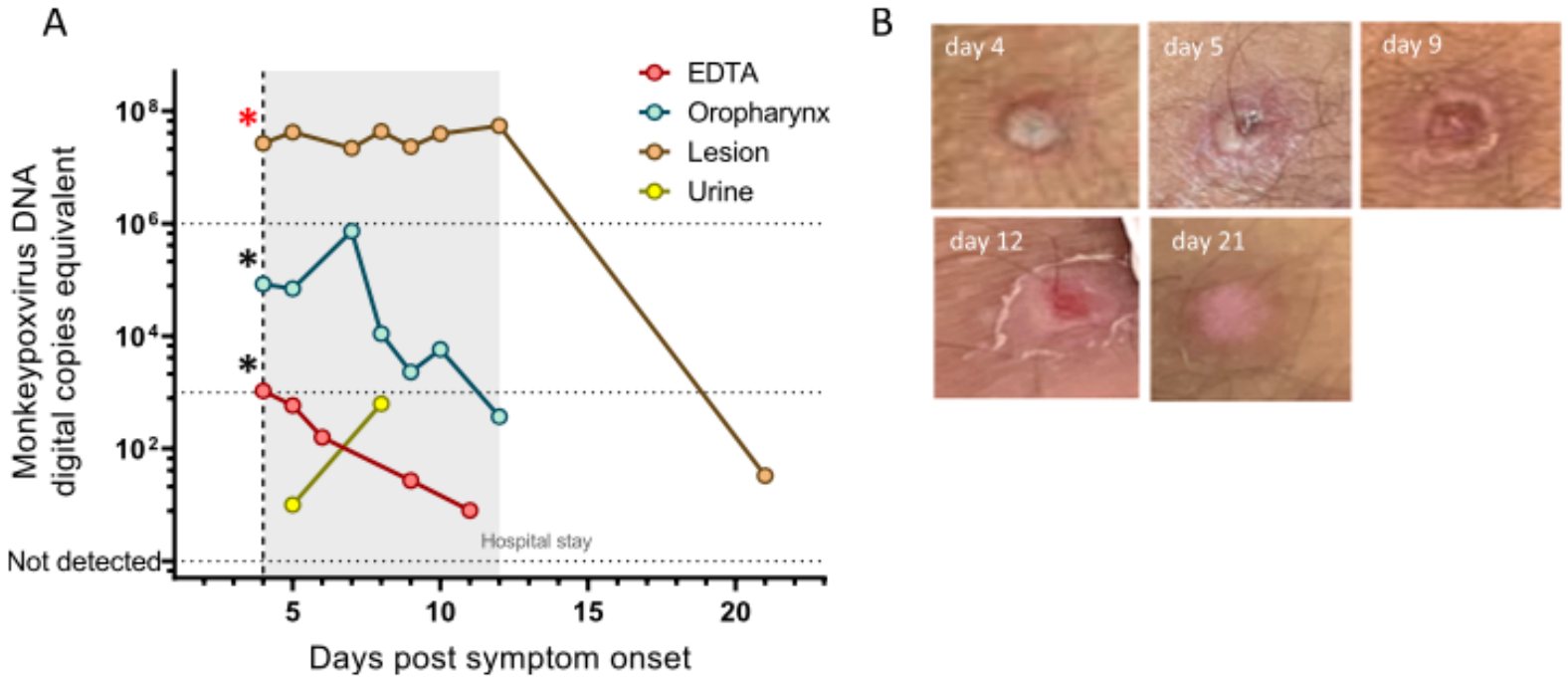


Fig. 2. A) Viral DNA-loads of different specimen types are plotted for patient 1. gray area represents their stay in the hospital. Red asterisk (*) represents a sample with successful isolation of infections virus, whereas black asterisks (*) represent unsuccessful attempts at viral culture. B) The evolution of an exemplary pustula is displayed over the same timeframe.

Nörz D. J Clin Virol. 2022 Oct;155:105254. PMID: 36057206