



TNX-801: Candidate Vaccine for Smallpox and Mpox based on Horsepox Virus (HPXV)

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of Science**
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Smallpox Vaccines: Lessons from COVID-19 and Mpox

Vaccines are essential

- Therapeutics are not a replacement – at best supplemental

Single dose vaccines have advantages

- One dose eliminates dropout between doses; potentially improves on real-world (RW) vaccine effectiveness
- Limits constraints on distribution system and public adherence

Durable protection and ability to block forward transmission are required to contain respiratory pathogens

- Live replicating vaccines for smallpox have these properties
- Unclear if other platforms such as mRNA vaccines can elicit life-time immunity

Continuing R&D and preparedness are important

- Modifying vaccine delivery and dosing during an outbreak may impair response

In 1796, Dr. Edward Jenner Introduced Vaccination to Protect Against Smallpox

Jenner observed that “vaccinia” was transmitted from horses to cows by farriers¹

- NextGen Sequencing has shown **horsepox virus** was used as a vaccine during the 19th century^{2,3}
- Potential **horsepox vaccine for smallpox** TNX-801 from synthetic biology under development⁴

- **Current administration**

- Bifurcated needle
- Percutaneous
- No sterile injection required



- **Biomarker of protection**

- Measure of T cell immunity⁶
- Described by Jenner
- Used in WHO accelerated eradication program



Take⁵



Microneedle Array Patch (MAP)

- Feasibility for horsepox under investigation

¹ Jenner E. "An Inquiry Into the Causes and Effects of the Variole Vaccinae, a Disease Discovered in Some of the Western Counties of England, Particularly Gloucestershire and Known by the Name of the cow-pox." London: Sampson Low, 1798.

² Schrick L et al. *N Engl J Med.* (2017) 377:1491-1492.

³ Souza ARV, et al. *mBio.* (2023) 14(5):e0188723. doi: 10.1128/mbio.01887-23.

⁴ TNX-801 is an investigational new biologic and is not approved for any indication

⁵ Centers for Disease Control and Prevention. Accessed April 15, 2020. <https://phil.cdc.gov/Details.aspx?pid=3276>

⁶ Fulginiti VA, et al. *Clin Infect Dis.* (2003) 37(2):241-250.

TNX-801 Immunogenicity and Efficacy in NHPs

- **Efficacy test in non-human primates (NHPs)¹**
 - “Take” observed
 - Limited replication at site of administration
 - No observable systemic replication
 - 100% protection



Article

Single Dose of Recombinant Chimeric Horsepox Virus (TNX-801) Vaccination Protects Macaques from Lethal Monkeypox Challenge

Ryan S. Noyce ¹, Landon W. Westfall ^{2,†}, Siobhan Fogarty ³, Karen Gilbert ², Onesmo Mpanju ⁴, Helen Stillwell ^{3,‡}, José Esparza ⁵, Bruce Daugherty ³, Fusataka Koide ², David H. Evans ¹, and Seth Lederman ^{3,*}

¹Noyce RS, et al. *Viruses*. (2023) 15(2):356.

TNX-801 Naturally Attenuated Relative to Vaccinia Vaccine Strains *in vitro*¹

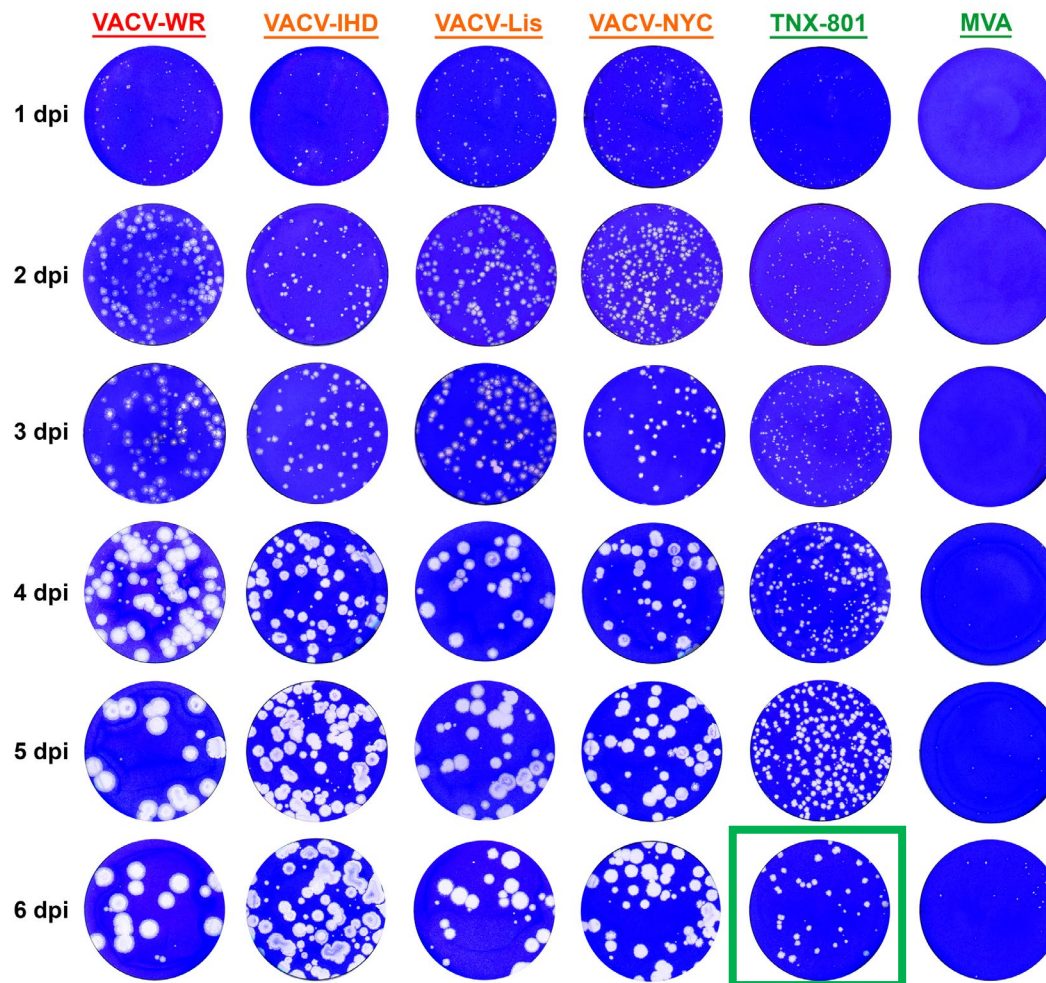
Vaccinia (VACV) Strains in Vero-E6 Cells

Propagation capacity:

Robust

Moderate Deficient

- TNX-801 *in vitro* **attenuated** relative to all VACV tested¹
 - Small plaque size
 - Similar to natural isolate²
 - Immortalized NHP cell lines:
 - Up to **119-fold**
 - Primary Human cells
 - 1) Dermal Track
 - 2) Respiratory Track
 - Up to **28- or 112-fold**

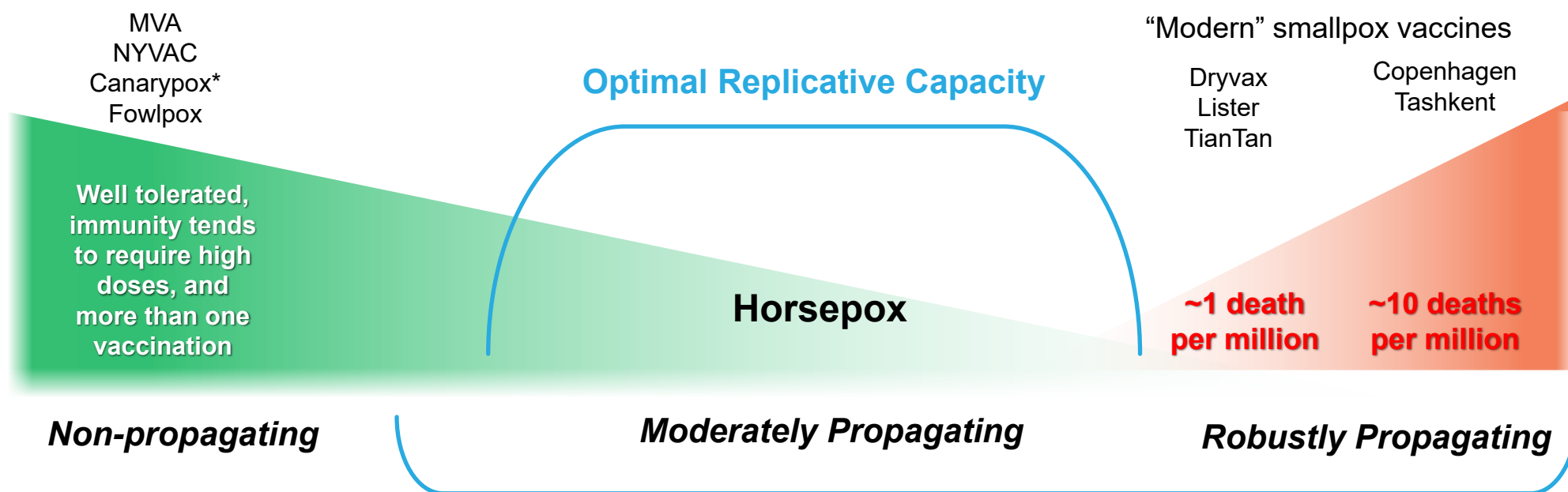


¹Trefry S, et al. *BioRxiv*. October 26, 2023.
doi: <https://doi.org/10.1101/2023.10.25.564033>

²Trindale GS et al. *Viruses*. 2016. (12). pii: E328.

The Balance of Tolerability and Reactogenicity for Pox-based Vaccines

Tonix believes that there is a potential for a product that marries the safety of attenuated pox vaccines with the benefits (immune protection and low dose) of replicating pox vaccines



*Canarypox was the prime vector in Thailand HIV vaccine trial RV144 with 31.2% efficacy (ALVAC-HIV)¹

¹Rerks-Ngarm S, et al., *N Engl J Med.* (2009) 361(23):2209-20.

Tonix Platform Selected by NIH/NIAID for Project NextGen COVID¹

 Nasdaq [Market Activity](#) [News + Insights](#) [Solutions](#) [About](#) [Nasdaq+](#)

Tonix Pharmaceuticals' Vaccine Candidate, TNX-1800, Selected by NIH/NIAID Project NextGen for Inclusion in Clinical Trials

PUBLISHED

NOV 2, 2023 8:00AM EDT

Feedback



NIAID is conducting early phase clinical trials on select next generation COVID-19 vaccine candidates with the intent to identify promising vaccine candidates

TNX-1800, a live virus percutaneous vaccine candidate, is based on Tonix's recombinant pox virus (RPV) platform

Phase 1 clinical trial of TNX-1800 expected to start in the second half of 2024

NIAID will cover the full cost of the clinical trial; Tonix will supply the vaccine candidate

¹TNX-1800 is an investigational new biologic and is not approved for any indication

Smallpox Vaccines: Proven Technology

Jenner's vaccine ("cowpox" [*sic*] / horsepox) controlled smallpox in Europe, US & other places 1800-1900¹

- Single dose
- Provides durable protection
- Blocks forward transmission
- Useful in post-exposure prophylaxis

Modern vaccinia (e.g., Dryvax, ACAM2000)

- Single dose
- Presumed descendant of Jenner's vaccine
- Effective in WHO accelerated eradication program
- Concerns about risk/reward in post-eradication era

Non-replicating/propagating vaccine (e.g., MVA)

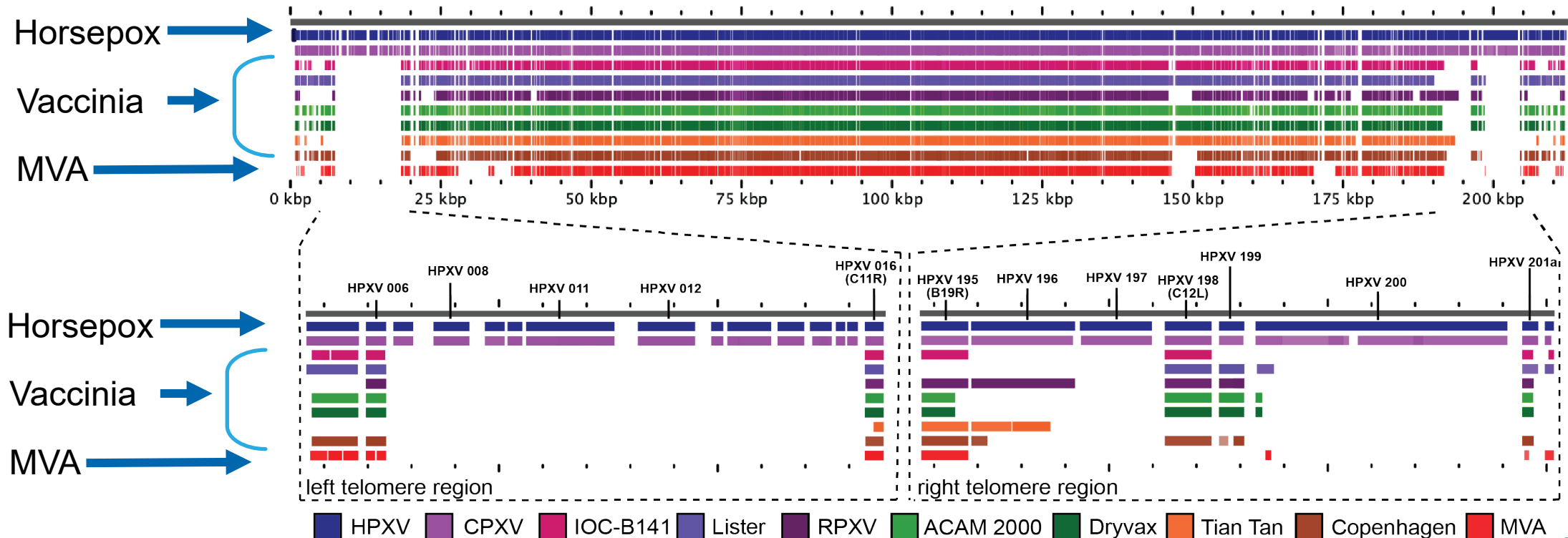
- Two doses
- Jynneos® (MVA-BN) approved for smallpox and monkeypox
- Safe in immuno-compromised (e.g., HIV⁺)
- Long term immune protection in humans unclear²

¹Souza ARV, et al. *mBio*. (2023) 14(5):e0188723.

²Zaack et al. *Nat. Med.* (2023) 29:270-278.

Alignment of Horsepox with Cowpox and Vaccinia-Based Vaccines¹

- Horsepox contains almost the full complement of genes from primordial cowpox
- Modern vaccinia viruses contain substantial deletions, particularly on the left and right sides near the inverted terminal repeats (ITRs)
- MVA contains deletions relative to modern vaccinia near the ITRs but also throughout the genome



¹Alignment was created using GView. Coding sequences with >80% homology to HPXV are shown in the alignment (with Permission Ryan Noyce, Univ. of Alberta.)

Horsepox and MVA – Attenuation Based on More or Less Genes

Virulence:

Virus:

Genetic alteration:

Selective Pressure:

attenuated

Horsepox



Deletions

Passage on Calf Skin (?)

robust replication

Modern Vaccinia



Deletions

Passage in Avian Cells

attenuated

MVA

1796 – Postulated Jenner's vaccine, ~1860 horsepox vaccines and 1976 horsepox¹⁻⁴

- Full complement of primordial “cowpox” genes
- Unaltered genome, no deletion of genes
- Attenuated – based on recent Tonix characterization

1976 – “Modern Vaccinia”

- Deletions on right and left sides (near ITRs)

1968 – MVA developed by selecting vaccinia for growth on avian cells^{5,6}

- Significant random deletions, including deletions of genes
- “Non-replicating” (or non-propagating) in human cells

¹ Schrick L et al. *N Engl J Med.* (2017) 377:1491-1492.

² Tulman ER, et al. *J Virol.* (2006) 80(18):9244-58.

³ Noyce RS, et al. *PloS One.* (2018) 13(1):e0188453.

⁴ Souza ARV, et al. *mBio.* (2023) 14(5):e0188723.

⁵ Volz A, Sutter G. *Adv Virus Res.* (2017) 97:187-243.

⁶ Kennedy JS, Greenberg RN. *Expert Rev Vaccines.* (2009) 8(1):13-24.

Smallpox Risk and Potential Vaccine Benefits for the U.S. Public

U.S. Population is largely orthopox naïve

- Few Americans vaccinated since ~1972
- Potential asymmetric risk for US population relative to countries who continued vaccinia vaccination for certain populations (e.g., Russia)

Many more Americans are immunocompromised (IC) today than in 1972

- HIV⁺, cancer chemotherapy, anti-TNF α treatment (e.g., Humira®)

Smallpox vaccination likely protects against mpox

- Only Jynneos is licensed, but historically live virus vaccination appears to protect
- Mpox is a continuing challenge whether from the U.S. endemic or from evolving epidemics outside the U.S.
- MSM population is at higher risk
- Clusters continue to appear, including cases in vaccinated individuals

Safer live virus vaccine and spread of mpox could alter vaccine recommendations

- Given devastating consequences of smallpox reintroduction, a safer vaccine might make widespread vaccination a sound public health policy
- Widespread vaccination would protect IC adults by decreased transmission, could provide protection individual protection prior to subsequent immunosuppression

Global Vaccine Supply and Equity

- **Protecting global populations protects U.S.**
 - Mpox (including Clade 1) appears to be re-emerging in Africa after the cessation of routine smallpox vaccination
- **Optimal dosing and administration**
 - Single administration
 - Smaller dose of particles (for orthopox-based vaccines)
 - Potential to manufacture using standard technologies
 - Non-sterile administration (bifurcated needed/percutaneous)
- **Potential new formulations**
 - Microneedle array patch
- **Cost and supply chain**
 - Vaccines without requirement for ultra-cold shipping/storage
 - Long term stability in storage
 - Potential for WHO global stockpile for developing countries
 - Goal is to provide vaccine for countries currently without access

Contributors

- **Tonix**
 - Sina Bavari
 - Zeil Rosenberg
 - Scott Goebel
 - Farooq Nasar
- **U Maryland**
 - José Esparza
- **Univ. of Alberta**
 - Ryan Noyce
 - David Evans



THANK YOU



Tonix Pharmaceuticals

- NASDAQ traded, commercial stage biopharmaceutical company
- Focus: CNS (2 commercial drugs) and Infectious Disease
- Poxvirus–based Vaccine program:
 - **Mpox/Smallpox (TNX-801)**
 - Pre-IND review by Regulatory Agency (FDA): clear pathway forward for Phase 1 /2
 - **Next Generation COVID (TNX-1800)**
 - Pre-IND review by Regulatory Agency (FDA): clear pathway forward for Phase 1
 - **TB (TNX-4400)**



Infectious Disease R&D Center (RDC) – Frederick, MD

Accelerated development of vaccines and antiviral drugs
~48,000 square feet, A/BSL-2 and A/BSL-3



Advanced Development Center (ADC) – North Dartmouth, MA

Development and clinical scale manufacturing of biologics including vaccines
~45,000 square feet, BSL-2+

Proposed History of Smallpox Vaccines

Based on work of José Esparza & Colleagues¹⁻⁴

1796 – Jenner’s vaccine

- “Cowpox” – believed similar to virus that is called “horsepox” today
- Mostly arm-to-arm propagation; Vaccination contemporaneous with equination

1875 – Industrialization of vaccine production on calves (Vaccine Farm Industry)

- Passage likely applied evolutionary pressures on what was likely horsepox
- Manufacturing processes may have selected for higher virulence

1967 – WHO selected 4 vaccines for eradication program (“Modern Vaccinia”)

- Russian EM-63, UK Lister, US New York City Board of Health, and the Chinese Temple of Heaven

2017 – Horsepox developed as smallpox/monkeypox vaccine

- Field isolate from 1976, sequenced by USDA scientists 2006, synthesized in 2018, shown efficacious in protecting against lethal MPXV challenge in 2019, attenuation characterized in 2023⁵⁻⁸
- Horsepox is believed closer to Jenner’s vaccine than “Modern Vaccinia”

¹ Schrick L et al *N Engl J Med* (2017) 377:1491-1492

² Esparza E, et al *Vaccine*. (2017) 35(52):7222-7230.

³ Esparza J et al. *Vaccine*. (2020) 38(30):4773-4779.

⁴ Souza ARV, et al. *mBio*. (2023) 14(5):e0188723.

⁵ Tulman ER, et al. *J Virol*. (2006) 80(18):9244-58.

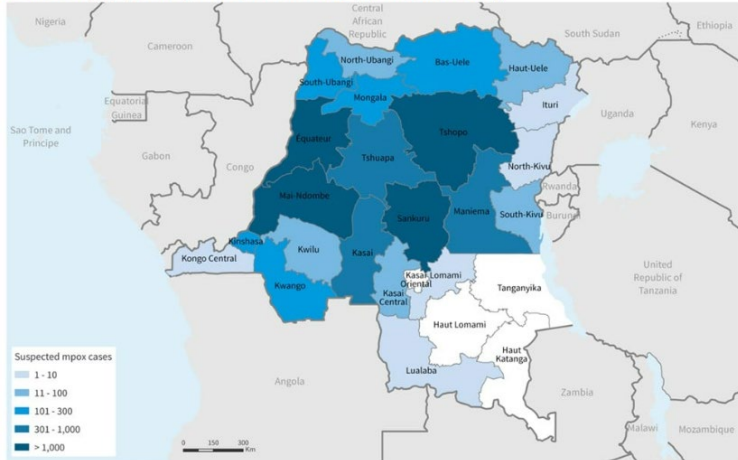
⁶ Noyce RS, et al. *PloS One*. (2018) 13(1):e018845.

⁷ Noyce RS, et al. *Viruses*. (2023) 15(2):356.

⁸ Trefry S, et al. *BioRxiv*. October 26, 2023. doi: <https://doi.org/10.1101/2023.10.25.564033>

Mpox remains a threat in Sub-Saharan Africa and Beyond

Figure 1: Geographic distribution of suspected mpox cases by province, Democratic Republic of the Congo, 1 January – 4 November 2023 (Epi weeks 1 to 44)



Orthopoxvirus Serosurvey Western Kenya
Kenya Medical Research Institute (KEMRI)
Mwau M, et al (2023)

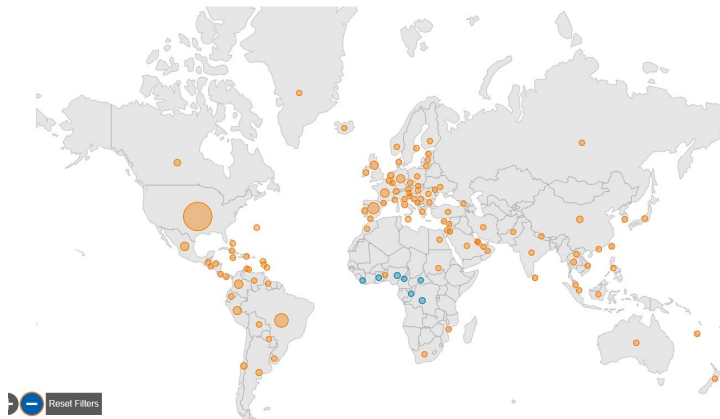
N=1624

N=962 <50 years

IgG+131(8.1%)

- IgG+/IgM+ 19 (14.5%)
- None reported prior smallpox vaccination.

Completed with Tonix Support to KEMRI



Mpox reported from 13 African Union member states

WHO <https://www.who.int/emergencies/disease-outbreak-news/item/2023-DON493>
accessed 11/29/2023



WHO 'very worried' about spread of mpox in DRC

Jennifer Rigby

Fri, December 8, 2023 at 7:41 AM EST · 2 min read

