Molecular Epidemiology of Human Mpox in Chicago

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Significance

Infections

Mpox (formerly known as monkeypox) is a syndrome of fever, rash, and lymphadenopathy caused by the mpox virus (MPXV), a zoonotic double-stranded DNA orthopoxvirus. Since its emergence in humans in the 1970's, MPXV has become endemic in central and western Africa.

Global Spread

In 2022, an outbreak of mpox consisting of over 88 thousand cases across 113 countries prompted the World Health Organization to declare a public health emergency of international concern. Cases in areas where the virus is not endemic are still occurring at a low frequency.

Prevention

High-risk populations for transmission were prioritized for vaccination with the JYNNEOS MPXV/smallpox vaccine.

Therapeutics

There is currently no FDA approved treatment specific for infections resulting from MPXV. The National Institute of Allergy and Infectious Diseases (NIAID) currently is enrolling patients for the Study of Tecovirimat for Human Mpox Virus trial (STOMP), which is designed to assess whether tecovirimat is safe and effective for the treatment of mpox in people with the disease. Some providers have been able to provide tecovirimat through the CDCs compassionate use guidelines.

New Transmission Routes

New research from the Democratic Republic of Congo has suggested that mpox cases belonging to clade I of the virus may now be transmitted through sexual contact. Previously, it was thought that only viruses belonging to clade II were able to spread through close contact. Clade I viruses typically have more severe disease and have a 10% fatality rate.

Transmission, treatment, and prevention

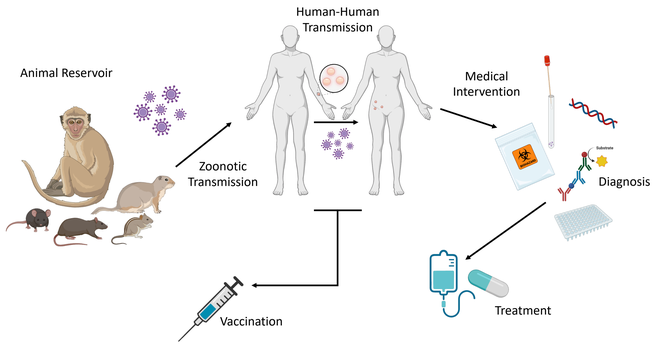


Figure 1 | Transmission of mpox virus, diagnosis, treatment and intervention. MPXV has many confirmed and potential animal reservoirs; in the case of zoonotic transmission a human can be exposed to an animal bite, bodily fluids or ingest contaminated meat. MPXV can also be transmitted human-to-human by exposure to bodily fluids or contact with skin lesions or mucosal membranes. Diagnosis of human mpox in the clinic involves the collection of swabs of the skin lesion and/or an ELISA to confirm the presence of antibodies to MPXV. Current treatment for mpox involve antibiotics, tecovirimat (TPOXX), and pain management with NSAIDS or opioids. JYNNEOS vaccinations are currently broadly available for the prevention of mpox and smallpox infections; however, the availability of these vaccines early in the outbreak period was erratic.

Research Focus & Strategy

Our goals in this project involve characterizing the 2022 outbreak in patients at Northwestern Memorial Hospital (NMH) in Chicago, as well as shedding light on the resurgence in 2023 in Chicago and continued low cases counts in places where the disease is not endemic.

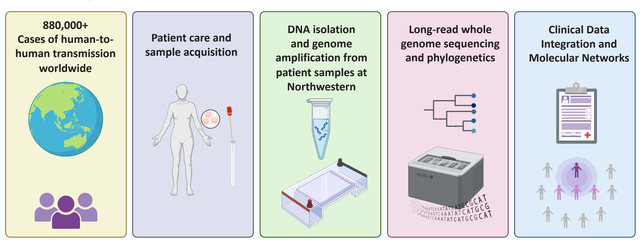


Figure 2 | Study Design Residual diagnostic specimens were obtained from Northwestern Memorial Hospital and affiliated clinics. Samples were entered into the MPXV Biobank at the Center for Pathogen Genomics and Microbial Evolution. Clinical data was retrieved for each specimen from the Northwestern Medical Enterprise Data Warehouse (IRB STU00217480). Viral DNA was extracted from each specimen and quality was assessed using a Nanodrop spectrophotometer. Viral genomes were amplified using 2 pools of alternating primers along the genome, developed at Yale in the Grubaugh Lab, commercially available from IDT. Libraries for sequencing were prepared then sequenced on the Nanopore GridION. Whole genomes were assembled and phylogenetic analysis was carried out.

2022-2023 Outbreak Epidemiology

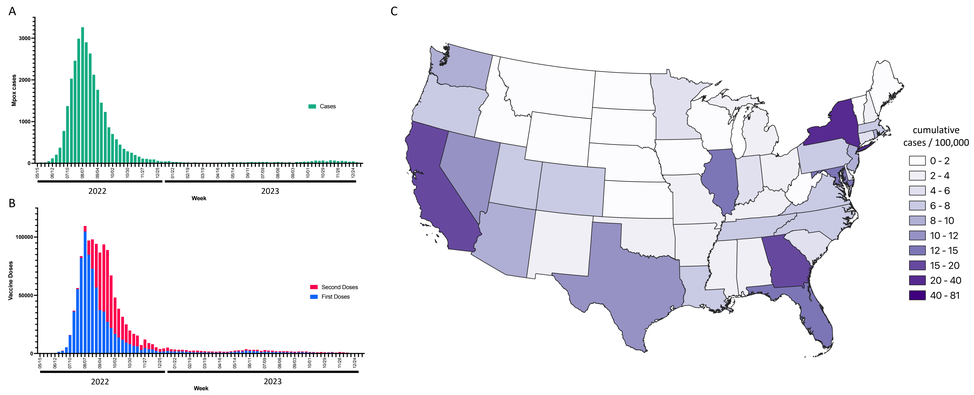


Figure 3 | Epidemiology of the 2022-2023 mpox outbreak in the US. **(A)** Weekly case counts in the US, case numbers peaked in August of 2022. **(B)** Weekly vaccine administration in the US **(C)** Map of the US showing cumulative cases per 100,000 people in each state. The highest case rate was in the District of Columbia at 81 cases per 100,000 people.

Cases at Northwestern Memorial Hospital

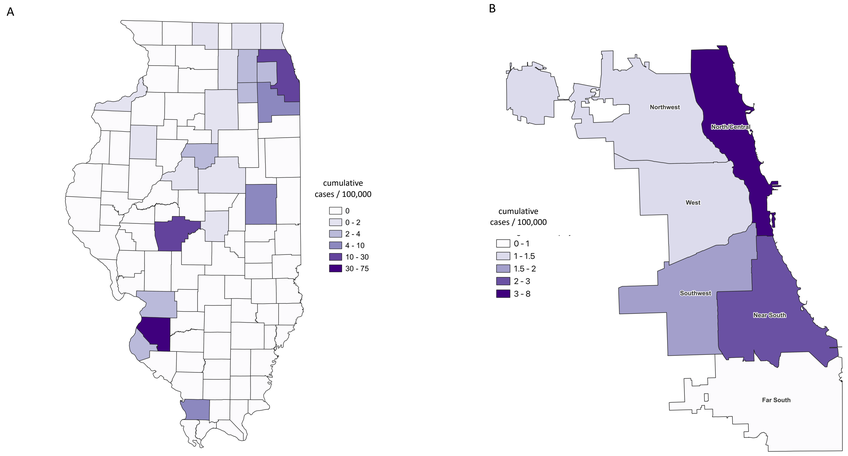


Figure 4 | Epidemiology of the 2022-2023 mpox outbreak at Northwestern Memorial Hospital. **(A)** Map of Illinois showing cumulative cases per 100,000 people in each county. Cook county, where NMH is located, recorded the highest number of cases in the state. **(B)** Map of Chicago showing the distribution of cases at Northwestern Memorial Hospital per 100,000 people in each region of the city.

Table 1

Variable	NMH Patients	Sequenced NMH Patients
Number	98	77
Age	33 (28, 40)	33 (28,40)
Gender		
Male	95 (97%)	77 (100%)
Female	1 (1.0%)	0 (0%)
Non-binary	1 (1.0%)	0 (0%)
Unknown	1 (1.0%)	0 (0%)
Race		
White	54 (55%)	43 (56%)
Black or African American	21 (21%)	17 (22%)
Unknown	19 (19%)	15 (19%)
Asian	2 (2.0%)	0 (0%)
Chinese	1 (1.0%)	1 (1.3%)
Filipino	1 (1.0%)	1 (1.3%)
Ethnicity		
Not Hispanic, Latino/a, or Spanish origin	69 (70%)	54 (70%)
Unknown	12 (12%)	9 (12%)
Hispanic or Latino	11 (11%)	10 (13%)
Another Hispanic, Latino, or Spanish origin	3 (3.1%)	1 (1.3%)
Mexican, Mexican American, Chicano/a	2 (2.0%)	2 (2.0%)
Puerto Rican	1 (1.0%)	0 (0%)
BMI	25 (23, 28)	25 (23,29)
PrEP for HIV	20 (21%)	18 (24%)
ART for HIV	23 (24%)	20 (26%)

[1]Median (IQR); n (%)

Table 2

Variable	2022	2023
All Patients	N=79	N=19
Vaccination	**11 (14%)**	**7 (37%)**
Zero doses	68 (86%)	12 (63%)
One dose	6 (8%)	2 (11%)
Two doses	5 (6%)	5 (26%)
Vaccine Administration Site (vaccinated population)	N=11	N=7
Subcutaneous	6 (55%)	4 (57%)
Intradermal	2 (18%)	2 (29%)
Subcutaneous/ Intradermal	3 (27%)	1 (14%)
Vaccine Administration (vaccinated population)	N=11	N=7
Prior to Infection	8 (73%)	7 (100%)
Average Days between vaccination and Infection	23	307
Post Infection	3 (27%)	0 (0%)
Average Days between vaccination and Infection	141	N/A

n (%)

Table 3

Variable	NMH Patients	Sequenced NMH Patients
Number	98	77
Antibiotics	40 (42%)	32 (42%)
Tecovirimat	32 (33%)	23 (30%)
Opioids	16 (17%)	11 (14%)

[1]n (%)

Tables 1-3| Table 1 Demographics Study population demographics with a subset of samples for whole genome sequencing. **Table 2** Vaccination status and administration by year of outbreak. **Table 3** Treatments administered to study population.

Viral Diversity

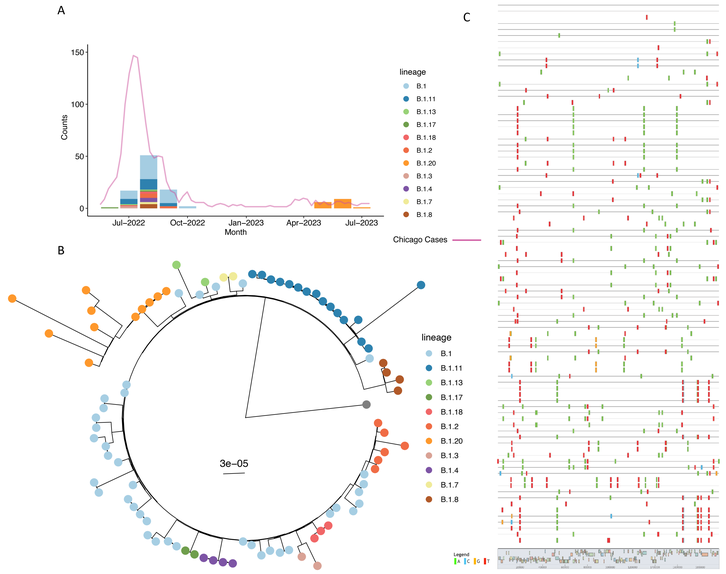


Figure 5 | Viral Diversity (A) The distribution of lineages from July 2022 to September 2023 in patient specimen sequenced from NMH overlaid with Chicago weekly cumulative case counts obtained from the Chicago Public Health Department. The outbreak in 2022 represented a diverse viruses circulating in the population. In contrast, the outbreak in 2023 saw the emergence of a singular clade in the NMH samples that most likely resulted from a large transmission cluster. **(B)** Phylogenetic diversity tree including 101 specimen from 77 patients in the study population. Specimen belonging to lineage B.1.20 are from 2023 and represent a unique transmission cluster. (B) Time tree constructed from sequences in the US. Sequences from Illinois, including those from this study, are highlighted in purple with indication lines. The 2023 Illinois cluster in the 11 o'clock position, highlighted in yellow, shows 10 specimens sequenced by the Chicago Health Department and 15 specimen from 13 patients sequenced at NMH, with the most likely common ancestor from Texas. **(C)** Highlighter plot depicting nucleotide mismatches comparing the NMH patient sequences to a mpox reference strain of lineage B.1.

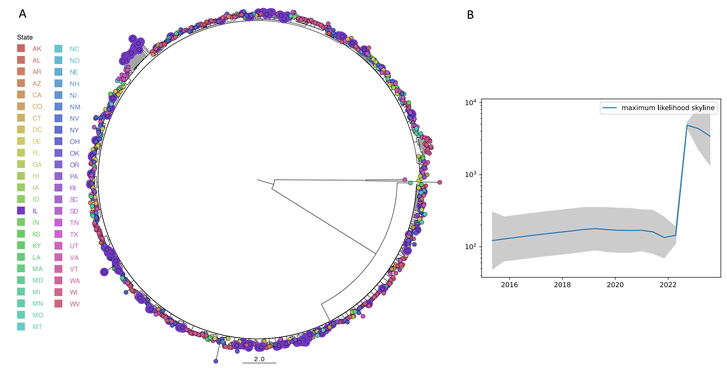


Figure 6 | Viral Diversity (A) Time tree constructed from sequences in the US. Sequences from Illinois, including those from this study, are highlighted in purple. The 2023 Illinois cluster in the 11 o'clock position, shows 10 specimens sequenced by the Chicago Health Department and 15 specimen from 13 patients sequenced at NMH, with the most likely common ancestor from Texas. **(B)** Skyline plot of population diversity showing the MPXV population changing over time using maximum likelihood (ML) estimation of population sizes through time. There is a steep increase in viral diversity in mid 2022, quickly tapering off into 2023. This is reflective of the lineage diversity observed in our study samples.

Summary of Findings

We observed a rapid increase in viral population size and diversity peaking in August 2022, comprised of eleven lineages, indicative of a high degree of viral circulation. On the contrary, all of the 2023 cases belonged to the same lineage, B.1.20, defined by three synonymous mutations. These most likely arose from a single transmission cluster, which was supported by traditional epidemiological follow up.

The circumstances underlying the unprecedented, international outbreak of mpox in 2022 remain to be fully elucidated. The reemergence of MPVX in 2023 suggests continued circulation in the human population, which is supported by the virus' continued evolution. Ongoing and robust epidemiological and genomic surveillance is required to determine if MPVX has become endemic in populations outside of West Africa. Continued monitoring of the genetic variation of the virus will allow for development of new antivirals and vaccinations with increased efficacy.

Data Sources and Funding

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