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Northwest Pathogen Genomics Center of Excellence

Situation Report: Could linkage of whole genome sequencing and case investigation data have supported the public health response to mpox in King County, Washington?

Public Health – Seattle & King County

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Summary

A retrospective pilot study linking whole genome sequencing and case investigation data from mpox cases was conducted between May and September 2022, in King County, to assess whether sequencing could have aided the public health response. Linked data were analyzed for 30% of mpox cases from the pilot period. Genomic analyses showed all sequences belonged to Clade IIb lineage B.1, but clustered into multiple sub-clades, suggesting multiple introductions to King County. Based on the retrospective assessment, routine and real-time whole genome sequencing (WGS) likely could have supported public health mpox response in three main areas: determining if cases were likely exposed locally or outside the region, investigating epidemiologic linkage between cases, and distinguishing between long-term chronic infection and reinfection when repeat diagnostic tests return positive.

Background

Prior to 2022, cases of mpox in the U.S. were associated with travel to endemic areas or transmission via imported animals.[1] As the 2022 global outbreak began, many cases reported neither of these exposures, raising questions about the transmission dynamics in this emerging outbreak.[2] Understanding mpox transmission dynamics is crucial for an effective public health response, and sequencing offered a complementary data source to examine transmission patterns that could enhance contact tracing and outbreak detection efforts.

The first reported mpox case in King County, Washington in the 2022 outbreak occurred in May 2022, and this pilot study focused on the period of high case volume from May 2022 through September 2022.[3] Mpox cases have continued beyond this time period, and as of December 2023 there were 563 cases of mpox reported in King County with 18 hospitalizations (3.4% of total cases). Monthly mpox cases in King County peaked in July 2022 with 220 new cases, followed by 165 cases in August 2022. Reported cases declined, then plateaued in subsequent months, with cases continuing to occur through the end of 2023, when this report was written (Figure 1).[3]

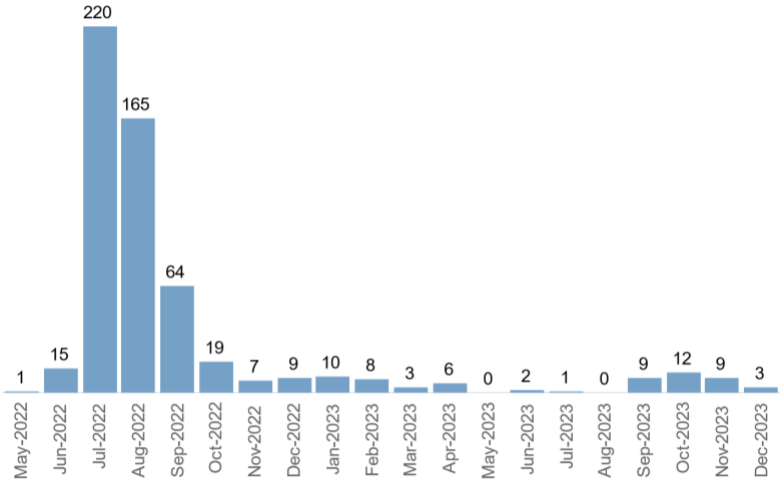

Figure 1. Count of mpox cases in King County by month of onset, May 2022 - December 2023

Approach

To assess how WGS could be combined with case investigation data to support public health action, the Washington State Department of Health (WA DOH) and Public Health—Seattle & King County (PHSKC) conducted a pilot, retrospective analysis of linked sequencing and case investigation data for mpox cases. The pilot focused on cases occurring in King County residents from May 1 through September 1, 2022. WGS was performed on residual diagnostic specimens by the University of Washington (UW) Virology Laboratory. Sequencing results were linked to cases by WA DOH, and detailed investigation data were obtained and added by PHSKC. Sequences were successfully obtained and linked to epidemiological data for 126 mpox cases (30% of total cases occurring in King County during the pilot study period).

WA DOH created a Washington-focused Nextstrain build to visualize a phylogenetic tree of the local cases along with background contextual sequences sampled from around the world. Using the Nextstrain metadata overlay feature, structured epidemiological data from case investigations were overlaid on the phylogenetic tree and analyzed jointly by PHSKC and WA DOH. When similar structured responses were observed for multiple sequences clustering closely within the phylogenetic tree, detailed free-text fields for those cases were reviewed further for common exposures or risk factors. For example, the tree could be color-coded based on "Yes/No" responses to "History of recent travel?" , and if several "Yes" responses were reported amongst sequences clustering together, we examined the longform free-text fields for those cases in search of possible common exposures such as travelling to the same places or interacting with each other. In this way, the combination of genetic similarity and

common reported exposures was used to generate hypotheses of epidemiologic relationships and trigger closer review.

While the sequenced cases represent a convenience sample and were not specifically selected for population representativeness, the demographics of the sequenced cases were generally similar to the demographics of cases overall. Hispanic/Latinx individuals had slightly greater representation in the genomic data, and residents of the city of Seattle had slightly lower representation. The full demographics of sequenced cases compared to all cases is given in the appendix (Table 1).

Findings

Through the pilot, we were able to assess genomic diversity and transmission dynamics of mpox in King County and identify ways WGS could have supported public health response if sequence data had been available in real-time. Three identified applications of genomic sequencing data were:

- Differentiating cases of outside introduction (e.g. travel-associated infections) from cases who likely acquired their infection locally, as part of transmission chains circulating in the county.
- Strengthening confidence in inferred epidemiologic linkages by utilizing both genomic information and case interview data.
- Distinguishing between long-term chronic infections and reinfections amongst individuals with repeat positive diagnostic tests.

WGS showed that all 126 sequences are descendants of Clade IIb lineage B.1. The presence of several subclades suggests multiple introductions of mpox into King County, which is consistent with travel history obtained through case interviews. Some clades grouped multiple sequences with identical or nearly identical genome sequences and showed an accumulation of mutations on top of a common background genotype, suggesting sustained community transmission after introduction (Figure 2). This type of phylogenetic analysis could support case investigations by supplementing reported travel history. For example, when a person reports recent travel, and phylogenetic analysis indicates a genotype without a common ancestor among other King County cases, it would strengthen the evidence that the travel-associated exposure was the likely source of their infection.

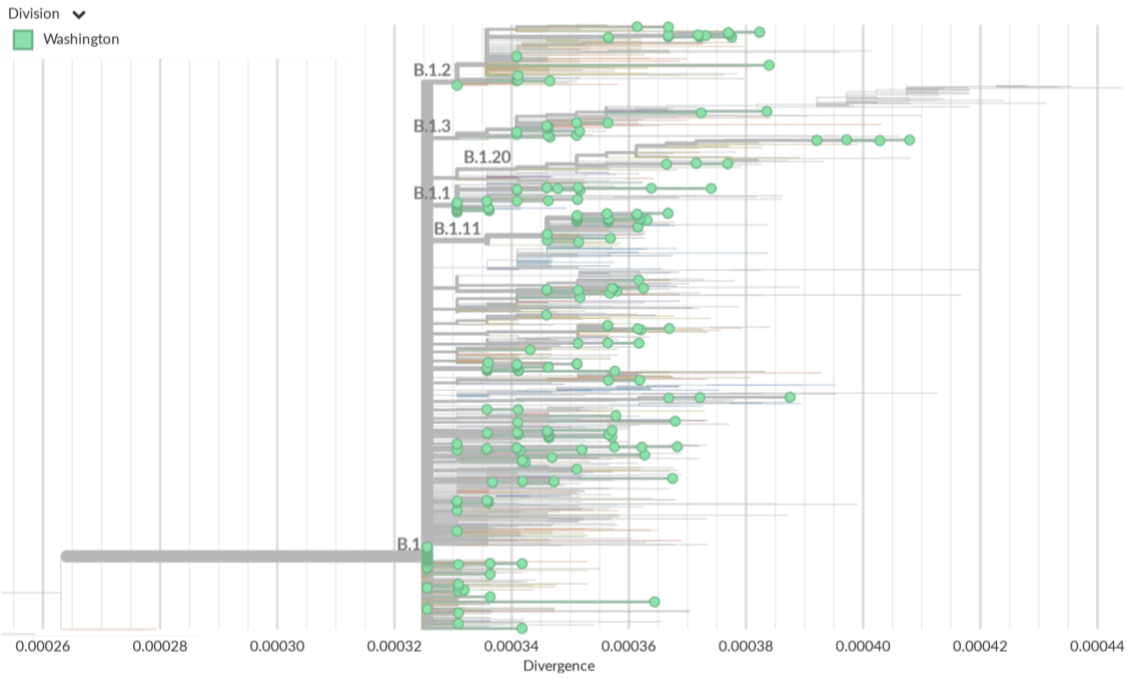

Figure 2. Phylogenetic tree of mpox sequences in Washington State-focused Nextstrain build. Sequences from Washington highlighted in green.

WGS also describes viral genetic similarity between individual cases' infections, measured as the number of single nucleotide polymorphisms (SNP) between sequences. These results could support public health investigations by strengthening confidence in inferred epidemiologic linkages. Among cases in the pilot classified during initial investigation as suspected clusters based on common reported exposures and onset dates, retrospective sequencing results supported those classifications. Where sequencing was available, cases within an epidemiologically-defined cluster were genetically similar, with no more than three SNPs separating the viral sequences sampled from those individuals. While genetic similarity does not confirm epidemiologic linkage, it adds supportive evidence. No clusters in the pilot study contained cases with sequences that were highly divergent, but this type of finding could also be useful for public health investigations as it would suggest the common reported exposure that led to the suspected epidemiologic linkage was not the source of infection for both cases. This finding could trigger follow-up interviews to identify the true exposures leading to infection.

Another potential application of linked epidemiologic and sequencing data is distinguishing between reinfection and chronic infection when a single case has multiple positive tests over time. Samples with highly similar genotypes, and with the later sample's genotype showing accumulated mutations on top of the initial sample's genotype, would suggest a chronic infection. In contrast, if two samples taken over time from the same case were genetically divergent from each other, with each sequence showing

genetic similarity to strains circulating in the community at the contemporaneous time point, it would suggest reinfection. That determination is useful for public health to identify if there was a second exposure event to understand and mitigate, or if the course of infection is longer than expected. There was at least one case in King County during the pilot period where WGS from multiple time points could have helped answer this question, but unfortunately no samples from the case were sequenced.

Conclusions and Implications

This pilot study demonstrated that genomic surveillance for mpox can be implemented at the local level and elucidated potential applications of these results for public health response. By increasing the reliability of inferences about where and when transmission likely occurred, sequencing could help public health agencies identify all exposed individuals to offer resources and strategies to prevent and mitigate mpox, such as vaccination, testing, and information on symptoms to watch for and when and where to seek treatment. WGS could also prompt collaboration across jurisdictions. For example, in the pilot study, a small cluster of sequences from King County was identified as genetically similar to sequences sampled from Massachusetts, suggesting a possible relationship between outbreaks occurring in these two states. If mpox sequencing had been available while these cases were being investigated, public health agencies from both states could have looked for large events that may have seeded outbreaks in both states. If an event was identified as associated with transmission, public health actions could be taken, such as collaborating with event organizers to message attendees encouraging them to monitor for symptoms, get vaccinated, and get tested, or issuing a health advisory to providers to consider mpox in patients who attended the event and encourage the same actions.

While mpox sequencing offers opportunities to support public health response, there is an important need for community engagement and assessment of implications for privacy given the overlap between transmission networks and sexual networks. This study began when transmission dynamics of mpox were still emerging. Now it is clear that sexual encounters are the most frequent form of transmission of mpox and that mpox disproportionately impacts men who have sex with men and people living with HIV.[4] Public health agencies interested in implementing mpox sequencing as part of their response work would be well served to look to examples of community outreach and engagement around use of genomics for HIV cluster detection and response[5] and to incorporate robust engagement with affected communities in their approach.

Appendix

Methodology Details

During the analysis period, around 50% of mpox cases in King County had diagnostic PCR testing performed at UW Virology Laboratory. Among these PCR-positive specimens, UW Virology attempted WGS on all specimens with a qPCR cycle threshold value below 31. WGS was performed using a hybridization probe-capture-based approach with probes designed using the MPXV 2022/MA001 strain as described previously.[6] UW Virology published sequences to GenBank and shared clinical accessions and collection dates with WA DOH to enable linkage of sequencing and case data. WA DOH was able to link 74% of mpox whole genome sequences to cases in the state disease surveillance database, known as the Washington Disease Reporting System.

The Washington-state focused Nextstrain build can be viewed publicly here: https://nextstrain.org/groups/waphl/wa/hmpxv1. Details on how the Nextstrain build was set up can be viewed publicly here: https://github.com/nextstrain/monkeypox.

Table 1. Demographics of all mpox cases during the pilot period of May 1 through September 1, 2022 versus cases with linked whole-genome sequences, King County, WA

	All cases (n=426)	Sequenced cases in pilot (n=126)
Age		
<18 years old	0-5%*	0-5%*
18-49 years old	89%	89%
50 years old and older	0-10%*	0-10%*
Sex (reported at time of diagnosis)		
Male	>95%	>95%
Female	0-5%*	0-5%*
Other	0-5%*	0-5%*
Unknown	0-5%*	0-5%*
City of residence		
Seattle	**76%**	70%
Other	No other city with more than 5%	No other city with more than 5%
Ethnicity (of any race)		
Hispanic/Latinx	26%	**30%**
Not Hispanic/Latinx	67%	66%
Unknown	7%	4%
Race (of any ethnicity)		

American Indian/Alaska Native	0-5%*	0-5%*
Asian	6.1%	0-5%*
Black/African American	9.9%	9.5%
Native Hawaiian and Pacific Islander	0-5%*	0-5%*
White	59%	60%
Additional Racial Identity	12%	13%
Unknown	8.5%	5.6%
Gender identity		
Cisgender male	17%	18%
Transgender male	0-5%*	0-5%*
Male (cis or trans unspecified)	78%	79%
Female (trans, cis, or unspecified)	0-5%*	0-5%*
Non-binary/genderqueer or Gender not listed	0-5%*	0-5%*
Unknown	0-5%*	0-5%*
Gender identity and gender of sexual partners[§]		
Men who have sex with men[†]	78%	76%
Men who do not have sex with men	18%	21%
Women who have sex with men[†]	0-5%*	0-5%*
Women who do not have sex with men	0-5%*	0-5%*
Additional genders who have sex with men[†]	0-5%*	0-5%*
Additional genders who do not have sex with men	0-5%*	0-5%*
Unknown	0-5%*	0-5%*

*Exact numbers not shared to protect privacy.

[§]For the purpose of this question, men indicates all individuals who identify as male, including trans, cis, or unspecified identity. Women indicates all individuals who identify as female, including trans, cis, or unspecified identity. Additional genders indicates all terms listed above under "Additional diverse terms."

[†]This total includes both individuals who have sex with men only, and individuals who have sex with men and with people with other gender identities.

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