

# HAWAII STATE DEPARTMENT OF HEALTH

## Wastewater Surveillance Report

11/26/2024

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# 1 Wastewater Surveillance of SARS-CoV-2

Wastewater-based epidemiology (also known as wastewater surveillance or sewer monitoring) has become an effective method for monitoring various pathogens to obtain unbiased data on disease prevalence in a community. Wastewater surveillance gained widespread recognition starting in 2020 as an effective early warning system for detecting community levels of SARS-CoV-2.

This has become especially helpful for tracking community levels due to the shift to self-testing and decreased clinical testing, reported COVID-19 case counts are lower than the *actual* COVID-19 case counts. Using wastewater surveillance data paired with the monitoring of COVID-19 case counts, hospitalizations, and fatalities allows for a more complete understanding of disease patterns. When trends are similar across these measures, confidence in the accuracy of those trends increases.

**Advantages** of monitoring wastewater concentrations of SARS-CoV-2:

- Wastewater based epidemiology:
  - Helpful when paired with clinical data since SARS-CoV-2 concentrations in sewage are positively correlated with COVID-19 case counts.
- Early warning for emerging outbreaks:
  - Infected people begin shedding 2 - 3 days before onset of symptoms.
  - SARS-CoV-2 is shed in feces by both individuals with asymptomatic and symptomatic COVID-19 infections.

**Possible limitations** of these data to consider:

- We cannot precisely predict case counts with the detection of concentrations of SARS-CoV-2 in wastewater.
- Wastewater surveillance might not capture low levels of infection in a community.
- Some communities and/or facilities are not connected to a Wastewater Treatment Plant (WWTP).
- Inhibitors could be present in wastewater that impacts the detection of SARS-CoV-2. Inhibition assessments are in place to ensure RNA quantification methods and viral recovery are performing as expected.

## Interpretation of Trends

For visualization and interpretation of trends, this report includes regression lines to help visualize possible changes in SARS-CoV-2 concentrations in sewage and COVID-19 case counts over time. For example, if the constant trend in SARS-CoV-2 concentrations is decreasing, we will likely observe a similar decrease in COVID-19 cases. Still, trends in concentrations do not always perfectly reflect community levels of SARS-CoV-2. Not all communities in Hawaii are sewered or are serviced by participating WWTP, which can disproportionately reflect more urban and often more heavily touristed areas. Tourism also frequently changes populations served by each WWTP and their travel may result in fluctuations in disease detection.

Not all peaks and surges in concentrations will correlate with a community-wide increase in cases. Wastewater is a highly variable mixture where concentrations of all pathogens like SARS-CoV-2 may vary based upon time of collection, or collection methods of sewage. For example, concentrations can vary on whether the sample was a grab sample (only captures at one point of time) or a 24-hour composite sample (more longitudinal variability over time). If an upward trend is observed in the data, this might represent an increase in cases that has yet to be confirmed through case-based surveillance. Additional data is required to confirm whether this trend will persist.

## 2 SARS-CoV-2 and Beyond: Additional Wastewater Surveillance Data

Other pathogens, excluding SARS-CoV-2, such as fungal, bacterial, or viral pathogens are suitable candidates for wastewater surveillance. To be monitored effectively, pathogens must be excreted or shed by humans, present in detectable concentrations during an active infection, and incapable of replication in the environment outside of a host (e.g., sewage systems). Pathogens meeting these criteria, and of public health significance, can be surveyed similarly to SARS-CoV-2 concentrations in wastewater. Notable examples of pathogens that fulfill the requirements for wastewater surveillance include Influenza (commonly known as the “Flu”), Respiratory Syncytial Virus (RSV), Norovirus (NoV), MPOX (formerly known as monkeypox), and *Candida auris*.

### Respiratory Pathogens

Influenza viruses are highly contagious enveloped RNA viruses that infect the upper respiratory tract and are always accompanied by a fever. The two common strains, Flu A and Flu B, are responsible for the majority of human infections during flu seasons. Infected individuals shed Influenza virus in bodily fluids like mucus and saliva for about 3 - 7 days in healthy adults, and up to 10 days or more in children depending on the viral titer. Infected individuals can also shed Influenza in their feces. Due to this viral shedding, Flu A and Flu B are deemed suitable for wastewater monitoring purposes. Additionally, two subtypes of Flu A (H3 and H5) are also surveyed in wastewater since they are of major public health concern.

Respiratory Syncytial Virus (RSV) is a single-stranded enveloped RNA virus that infects the respiratory tract with symptoms ranging from congestion, dry cough, fever, to trouble breathing. While RSV typically induces mild symptoms in healthy individuals, it poses a higher risk for severe infections in infants, the immunocompromised, and the elderly. RSV primarily spreads through large droplets or through contact with contaminated objects. Notably, the virus can survive on surfaces for several hours, potentially contributing to its spread. RSV has been detected in the stool of infected individuals, and its concentrations in wastewater have shown a significant positive correlation with clinically confirmed cases of RSV, demonstrating the effectiveness to track community prevalence of RSV with wastewater surveillance.

### Gastrointestinal Pathogens

Noroviruses (NoV) are single-stranded RNA viruses that cause millions of cases of acute gastroenteritis annually. Gastroenteritis is characterized by symptoms such as diarrhea, vomiting, nausea, and stomach pain and is commonly referred to as the “stomach flu.” Inadequate handwashing before touching the mouth or consuming food, ingestion of contaminated food or liquids from infected individuals, and consumption of uncooked shellfish are common routes of transmission. NoV is excreted in the feces of infected individuals regardless of infection severity, and does not replicate in the environment without a zoological host, making NoV an ideal candidate for wastewater surveillance. Current wastewater based epidemiology focuses on detection of two NoV genotypes, NoV GI and NoV GII, with NoV GII causing 80% of Norovirus infections worldwide.

### Other Pathogens of Concern

MPOX is a double-stranded non-variola *Orthopoxvirus* (NVO) that is closely related to smallpox. There are two clades of MPOX known as MPOX clade I and MPOX clade II. MPOX clade I has accounted for much less infections worldwide compared to clade II, but is more likely to cause severe illness and death especially in those who are immunocompromised. Infected individuals experience a painful rash resembling pimples or blisters, which can appear on various body parts such as hands, feet, chest, face, mouth, and genitalia. The virus primarily spreads through direct contact with infected individuals with an active rash, contaminated objects (fomites), respiratory droplets, or vertical transmission from a parent to child. MPOX can be shed from infected individuals into wastewater through urine, semen, saliva, and feces thus allowing community monitoring through wastewater surveillance. WBE of MPOX clade II began in 2022 in lieu of the global outbreak and has been useful in assessing the prevalence of this clade of MPOX within

communities. Additionally, surveillance has included the detection of NVO which can help determine the presence of either MPOX clade I or MPOX clade II, but does not distinguish between the two clades.

*Candida auris* (*C. auris*) is an opportunistic fungal pathogen known for its resistance to multiple antifungal agents. While *C. auris* generally poses minimal risk to healthy individuals, it significantly impacts individuals in long-term healthcare facilities, with underlying medical conditions, those with a history of exposure to antifungal agents, or patients requiring invasive medical devices. This pathogen primarily infects the skin through open wounds and the ears, often accompanied by fever and chills. However, *C. auris* may enter the body and infect the bloodstream, heart, or brain (similar to bacterial infections but do not improve with the use of antibiotics). Therefore, infections caused by *C. auris* can be severe and may lead to fatalities. While colonization with *C. auris* can occur without causing any noticeable symptoms, individuals can still transmit the pathogen to others through direct contact or contact with contaminated fomites. *C. auris* has been found in human excreta (feces and urine) as well as in wastewater. Utilizing routine wastewater surveillance to track new introductions of *C. auris* into specific jurisdiction's is vital for infection prevention and control efforts, especially in healthcare settings.

For more information on how wastewater surveillance works, refer to the resources at the end of the report.

### 3 National Wastewater Surveillance System (NWSS)

The following pages of this report contain results for the surveillance of sewage for SARS-CoV-2, Flu A, Flu A (H3N1), Flu A (H5N1), Flu B, RSV, and NVO in collaboration with the National Wastewater Surveillance System (NWSS). A total of 9 WWTP from the State of Hawaii are participating in this surveillance. Samples are collected weekly and analyzed by a contracted lab by NWSS (Verily). Due to the variability of wastewater and presence of inhibitors, concentrations reported have been normalized by flow and population served for each WWTP. Excessive rainfall and changes in water use can impact concentrations of SARS-CoV-2 in sewage over time. The use of a fecal indicator control (Pepper Mild Mottle Virus - PMMoV) helps account for any changes in human waste input in wastewater over time. Concentrations in this document are reported as log-transformed SARS-CoV-2 copies per liter of wastewater (unless otherwise stated).

Since SARS-CoV-2 is a constantly evolving virus, NWSS also collects information on the estimated composition of SARS-CoV-2 variants in wastewater. The detection of SARS-CoV-2 variants in wastewater is another useful layer of surveillance since some variants spread more rapidly than others. Information on dominant or new variants in a community assists in public health response. Additionally, in some cases, variants have been detected in wastewater prior to detection in clinical samples.

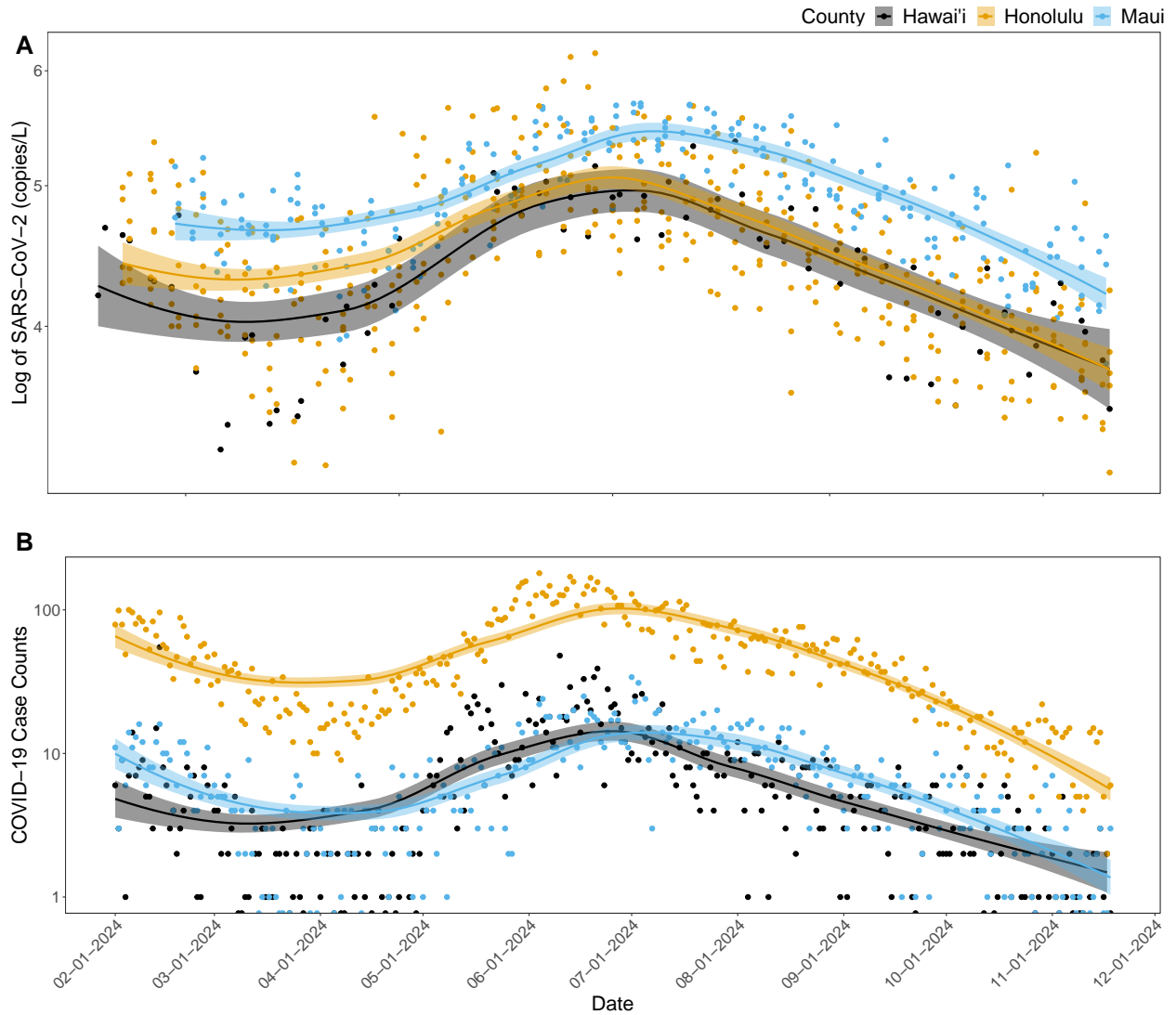
NWSS utilizes Next Generation Sequencing (NGS) to gather information on SARS-CoV-2 variants in wastewater. NGS is parallel to Whole Genome Sequencing (WGS) and allows for high-throughput and timely results. The estimated proportion of variants are calculated with the Freyja tool by measuring the frequency of variations at each position in the SARS-CoV-2 genome among mapped sequence fragments from a mixed SARS-CoV-2 sample. Data are reported in relative abundance. For example, if BA.5 (parent Omicron lineage) has the highest proportion, this means that BA.5 is the dominant variant relative to all other SARS-CoV-2 variants detected in the wastewater. These sequence data do not include information on the relative abundance of other pathogens present in wastewater. Variant composition estimates should be interpreted with caution, as substantial gaps in coverage across the reference genome and/or a lack of sequencing depth can produce inaccurate variant/lineage calls.

Please see previous reports for historical relative variant proportions from 07/01/2022 to 09/22/2023.

#### Metadata for participating WWTP by county

County	Number of WWTP	Total Estimated Population Served
Honolulu	5	906,000
Maui	3	157,700
Hawaii	1	32,604

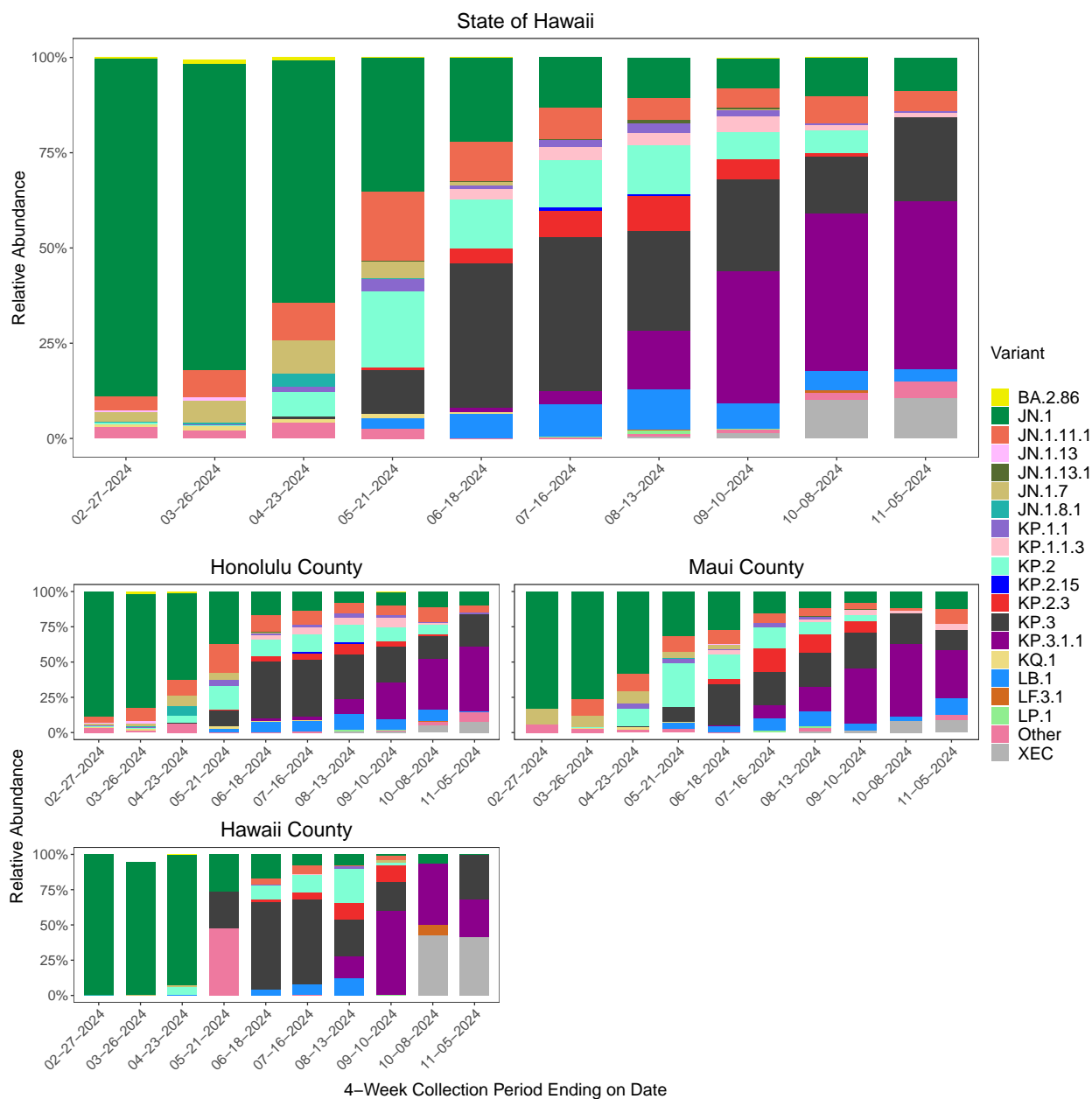
### 3.1 NWSS: SARS-CoV-2 Wastewater Surveillance Data



**Figure 1.** (A) Log transformed normalized concentrations of SARS-CoV-2 in sewage (copies/L) and (B) case counts for the State of Hawaii for Hawaii, Honolulu, and Maui counties from 02/01/2024 to 11/07/2024. Regression line was created with a prediction interval from a locally weighted (LOESS) regression. Shaded region represents 95% confidence interval.

**Notes:** Trends in raw sewage concentrations of SARS-CoV-2 are fluctuating in all counties. SARS-CoV-2 wastewater concentrations and COVID-19 cases are relatively stable in recent data.

## 3.2 NWSS: SARS-CoV-2 Variants Wastewater Surveillance Data

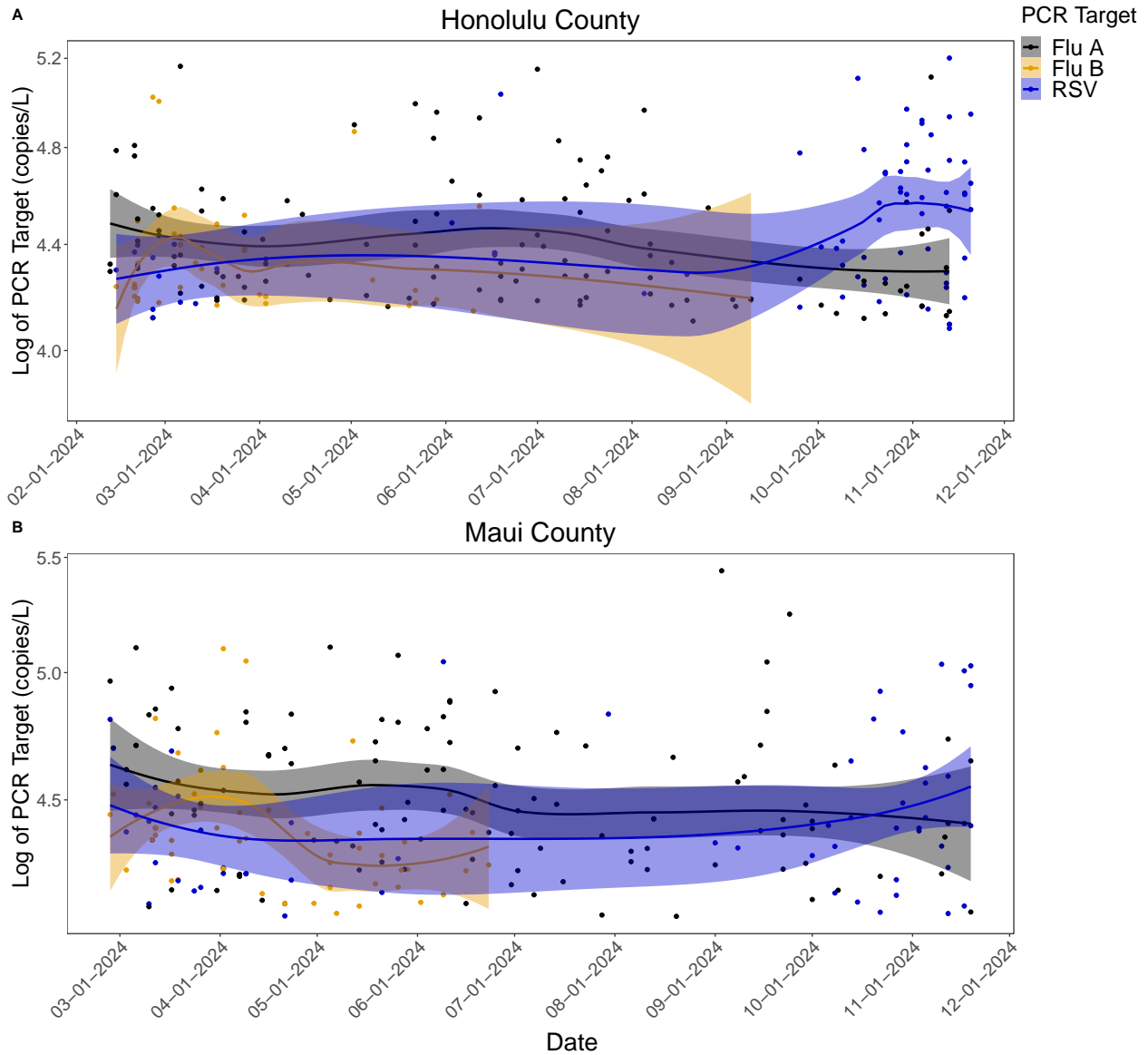


**Figure 2.** Stacked barplot demonstrating the relative abundance of SARS-CoV-2 aggregated lineages detected in wastewater across the State of Hawaii from 02/13/2024 to 11/05/2024.

**Notes:** Among the SARS-CoV-2 lineages detected in the most recent data included in this report, JN.1 lineages have the highest relative abundance of estimated variants since February 2024 across the State of Hawaii. For a more detailed description of sequencing and information on clinical SARS-CoV-2 variants in the State of Hawaii, refer to the *State of Hawaii SARS-CoV-2 Sequencing and Variant Report* and the resources provided at the end of this report. These data are only a partial representation of the population from each county which might impact the abundance of certain lineages.

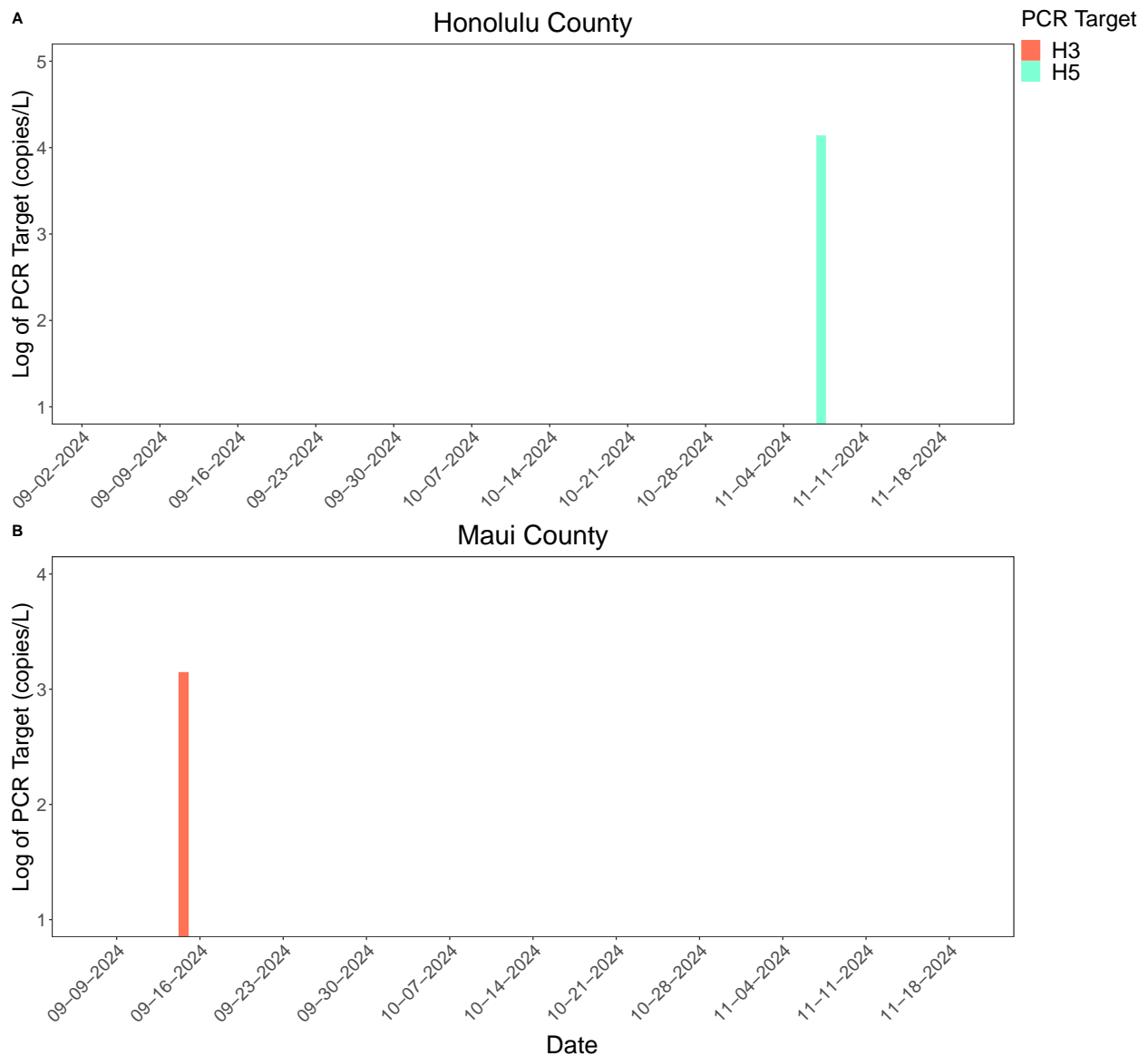


### 3.3 NWSS: Respiratory Pathogens Wastewater Surveillance Data



**Figure 3.** Log transformed normalized concentrations of Flu A, Flu B, and Respiratory Syncytial Virus (RSV) in sewage from (A) Honolulu County and (B) Maui County WWTP's over time from 03/01/2024 to 11/20/2024. Regression line created with a prediction interval from a locally weighted (LOESS) regression. Shaded region represents 95% confidence interval. Values below the limit of detection (LOD) are reported as 0 copies/L.

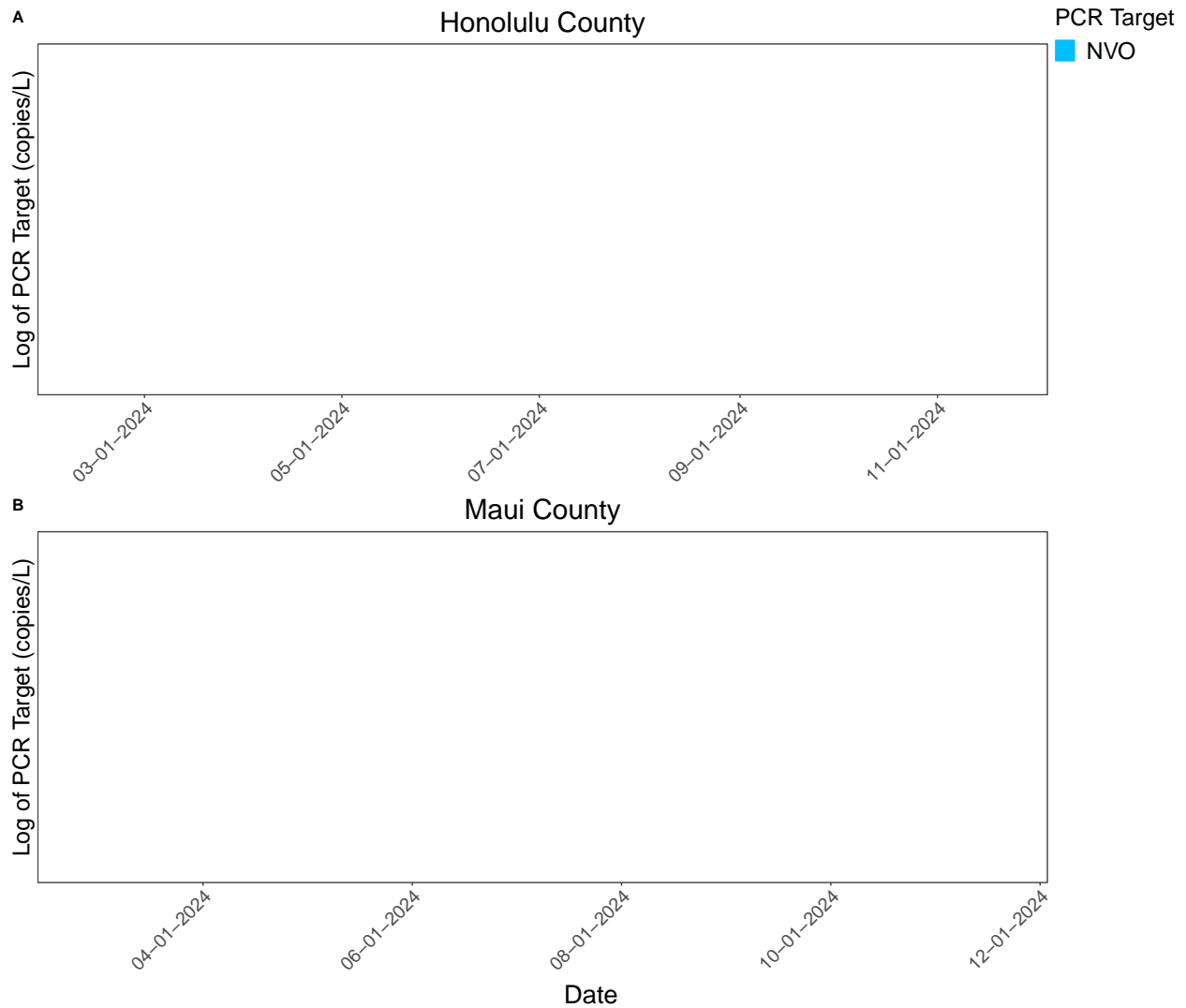
**Notes:** Across both counties, concentrations of all respiratory pathogens are fluctuating. There is currently insufficient data on Flu A, Flu B, and RSV in sewage for Hawaii County.



**Figure 4.** Bar chart of log transformed normalized concentrations of two Flu A subtypes, H3 (H3N1) and H5 (H5N1), in sewage (copies/L) from (A) Honolulu County and (B) Maui County WWTP's over time from 09/09/2024 to 11/20/2024.

**Notes:** Samples that fall below the limit of detection (LOD) are reported as 0 copies/L and do not appear on the figure. There is currently insufficient data on H3 and H5 in sewage for Hawaii County. There was a positive detection of H3 from a Maui County WWTP from a sample collected on 09/15/2024. H5 was detected for the first time in Hawaii from a sample collected at a Honolulu County WWTP on 11/07/2024. The detection of H5 in wastewater does not distinguish the subtype of H5. Although after further investigation, it was determined that birds near the Honolulu County WWTP were also infected with H5N1 (highly pathogenic avian influenza, HPAI). The Hawaii Department of Health State Laboratories Division (SLD) is continuing to investigate this detection by testing wastewater from this WWTP for H5. SLD will continue the wastewater surveillance and closely monitor for any detections in the future.

### 3.4 NWSS: Other Pathogens of Concern Wastewater Surveillance Data



**Figure 5.** Bar chart of log transformed normalized concentrations of non-variola *Orthopoxvirus* (NVO) in sewage (copies/L) from (A) Honolulu County and (B) Maui County WWTP's over time from 02/01/2024 to 11/20/2024.

**Notes:** Samples that fall below the limit of detection (LOD) are reported as 0 copies/L and do not appear on the figure. There have been no positive detections of NVO in sewage based upon data provided by NWSS. There is currently insufficient data on NVO in sewage for Hawaii County.

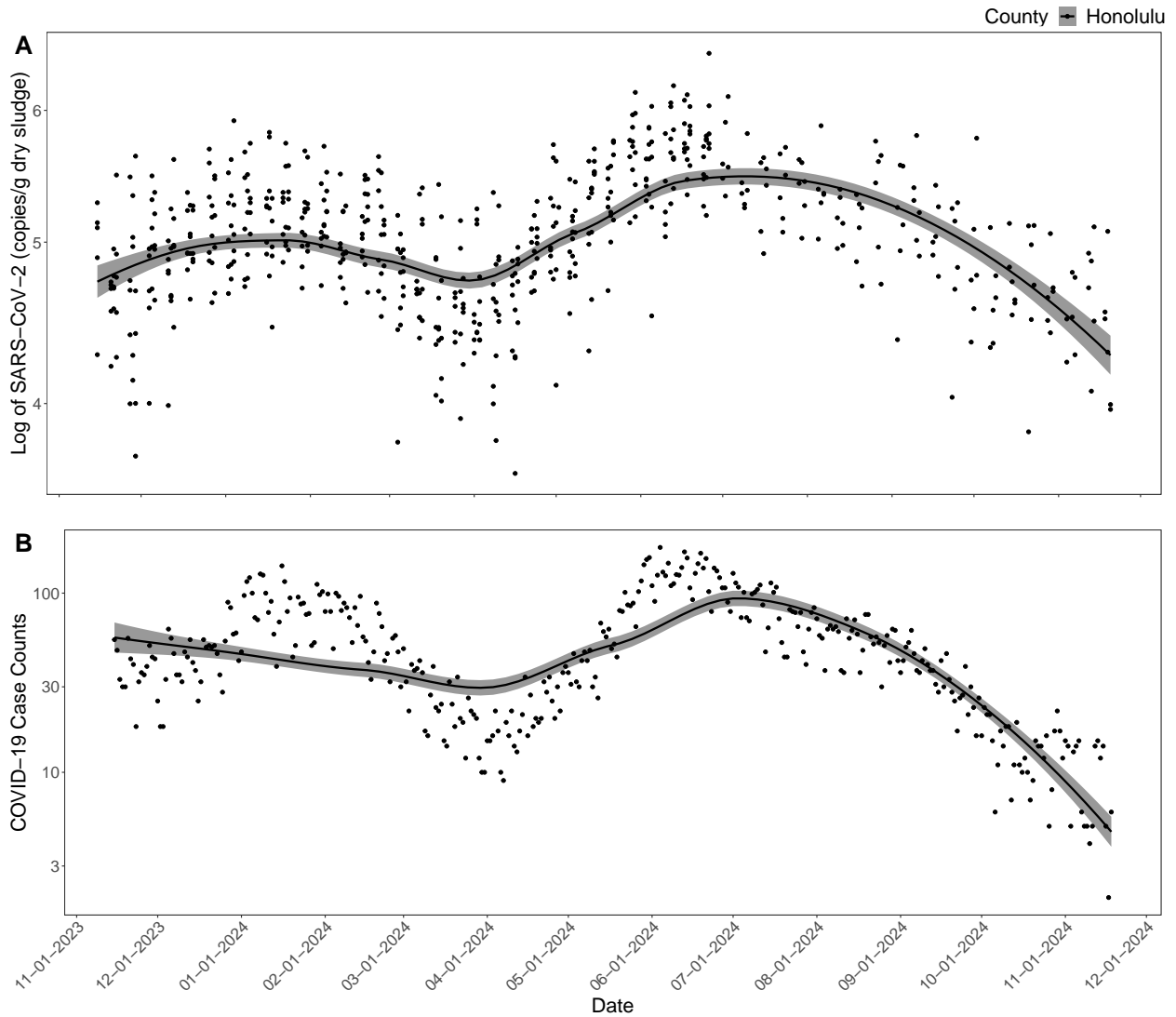
## 4 WastewaterSCAN

The following pages of this report contains results for wastewater surveillance of SARS-CoV-2, Flu A (including Flu A subtype H5N1), Flu B, Respiratory Syncytial Virus (RSV), Norovirus (NoV) genotype GII, MPOX clade II and *C. auris* in collaboration with the National Wastewater Surveillance System (NWSS) and WastewaterSCAN. **Note: two WWTP from the State of Hawaii are actively participating in this surveillance with WastewaterSCAN.** Samples are collected three times a week and analyzed by WastewaterSCAN. WastewaterSCAN processes sludge from participating WWTP in Hawaii rather than the liquid fraction. Concentrations of each target quantified by WastewaterSCAN are reported as log-transformed copies per g of dry sludge.

### Metadata for currently participating WWTP by county

County	Number of WWTP	Total Population Served
Honolulu	2	690,000

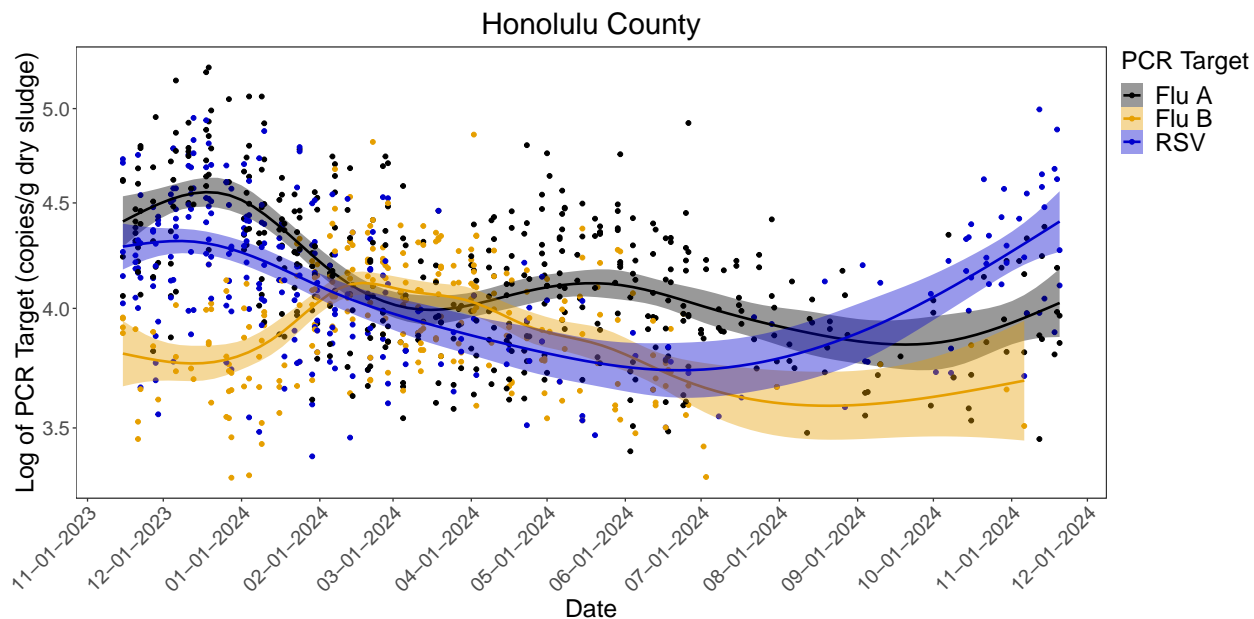
## 4.1 WastewaterSCAN: SARS-CoV-2 Wastewater Surveillance Data



**Figure 6.** (A) Log transformed normalized concentrations of SARS-CoV-2 in sewage (copies/g dry sludge) quantified by WastewaterSCAN for two WWTP in Honolulu County and (B) Honolulu County COVID-19 case counts from 11/15/2023 to 11/20/2024. Regression line was created with a prediction interval from a locally weighted (LOESS) regression. Shaded region represents 95% confidence interval.

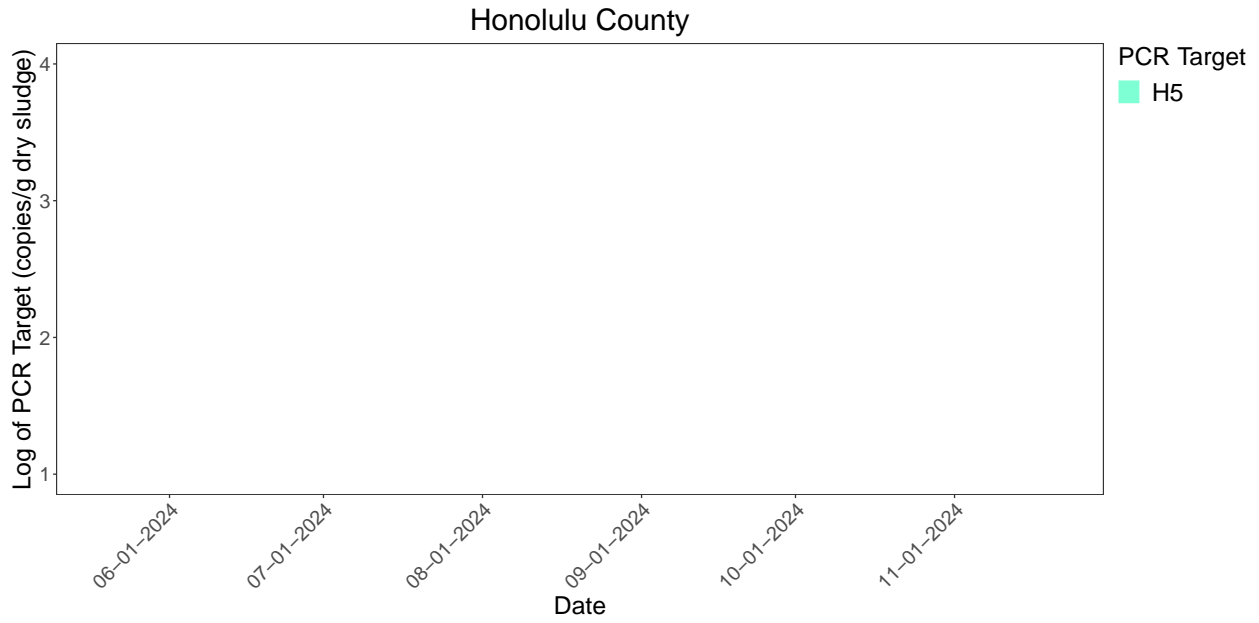
**Notes:** WastewaterSCAN has estimated that the limit of detection for targets is ~1000 copies/g. Trends in raw sewage concentrations of SARS-CoV-2 are fluctuating in this county. SARS-CoV-2 wastewater concentrations and COVID-19 cases are decreasing in recent data.

## 4.2 WastewaterSCAN: Respiratory Pathogens Surveillance Data



**Figure 7.** Log transformed normalized concentrations of Flu A, Flu B, and Respiratory Syncytial Virus (RSV) in sewage (copies/g dry sludge) quantified by WastewaterSCAN for two WWTP in Honolulu County from 11/15/2023 to 11/20/2024. Regression line created with a prediction interval from a locally weighted (LOESS) regression. Shaded region represents 95% confidence interval.

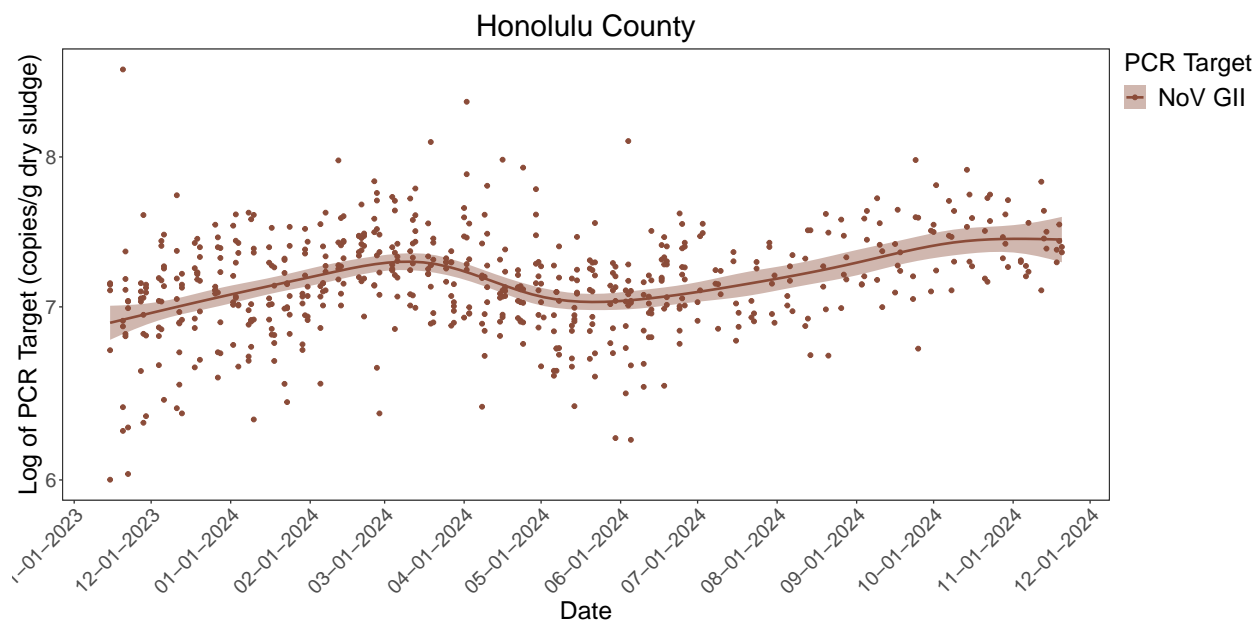
**Notes:** WastewaterSCAN has estimated that the limit of detection for targets is ~1000 copies/g. Concentrations of all respiratory pathogens are relatively stable in recent data.



**Figure 8.** Bar chart of log transformed normalized concentrations of Flu A subtype H5N1 (H5) in sewage (copies/g dry sludge) quantified by WastewaterSCAN for two WWTP in Honolulu County from 05/20/2024 to 11/20/2024.

**Notes:** WastewaterSCAN has estimated that the limit of detection for targets is ~1000 copies/g. Samples that fall below the LOD for H5 do not appear on the figure. There have been no positive detections of H5 in sewage based upon data provided by WastewaterSCAN.

### 4.3 WastewaterSCAN: Gastrointestinal Pathogens Wastewater Surveillance Data

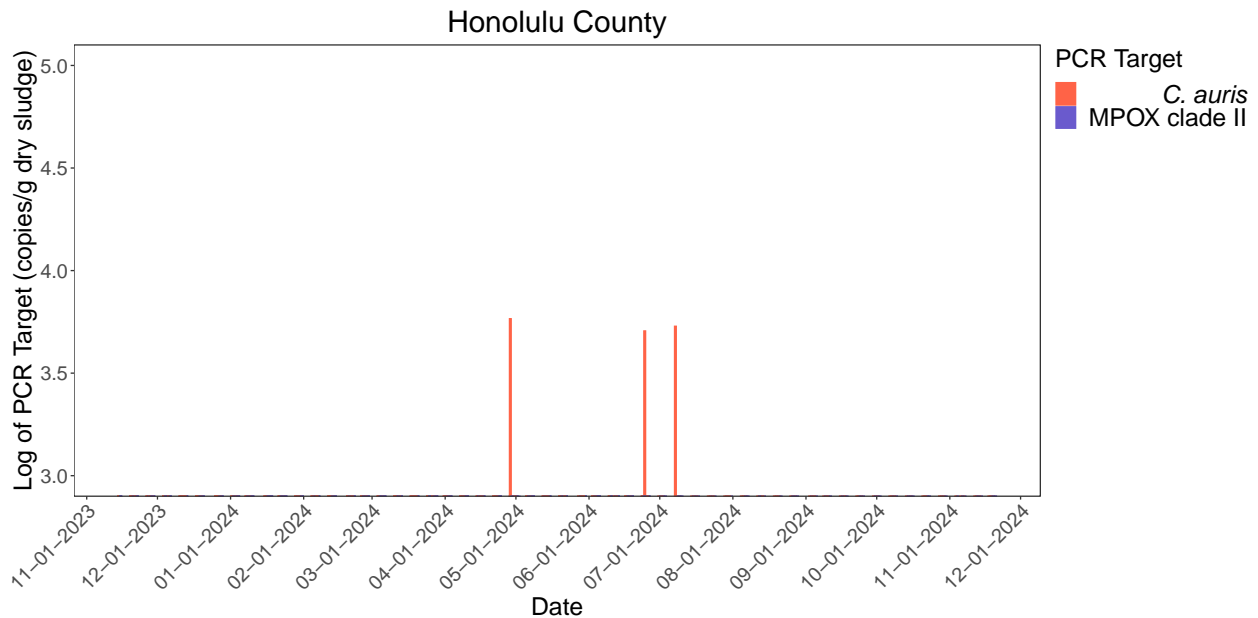


**Figure 9.** Log transformed normalized concentrations of Norovirus (NoV) GII in sewage (copies/g dry sludge) quantified by WastewaterSCAN for two WWTP in Honolulu County from 11/15/2023 to 11/20/2024. Regression line created with a prediction interval from a locally weighted (LOESS) regression. Shaded region represents 95% confidence interval.

**Notes:** WastewaterSCAN has estimated that the limit of detection for targets is ~1000 copies/g. NoV GII is found at consistently high concentrations compared to other pathogens likely since those infected primarily shed NoV GII in feces. Still, NoV GII trends are relatively stable across time in Honolulu County.



#### 4.4 WastewaterSCAN: Other Pathogens of Concern Wastewater Surveillance Data



**Figure 10.** Bar chart of log transformed normalized concentrations of *C. auris* and MPOX in sewage (copies/g dry sludge) quantified by WastewaterSCAN for two WWTP in Honolulu County from 11/15/2023 to 11/20/2024.

**Notes:** WastewaterSCAN has estimated that the limit of detection (LOD) for targets is ~1000 copies/g. Samples that fall below the LOD for *C. auris* and MPOX do not appear on the figure. Detection of MPOX and *C. auris* in samples is rare. There were multiple positive detections of *C. auris* in Honolulu County wastewater from samples collected on 04/29/2024, 06/25/2024, and 07/08/2024.

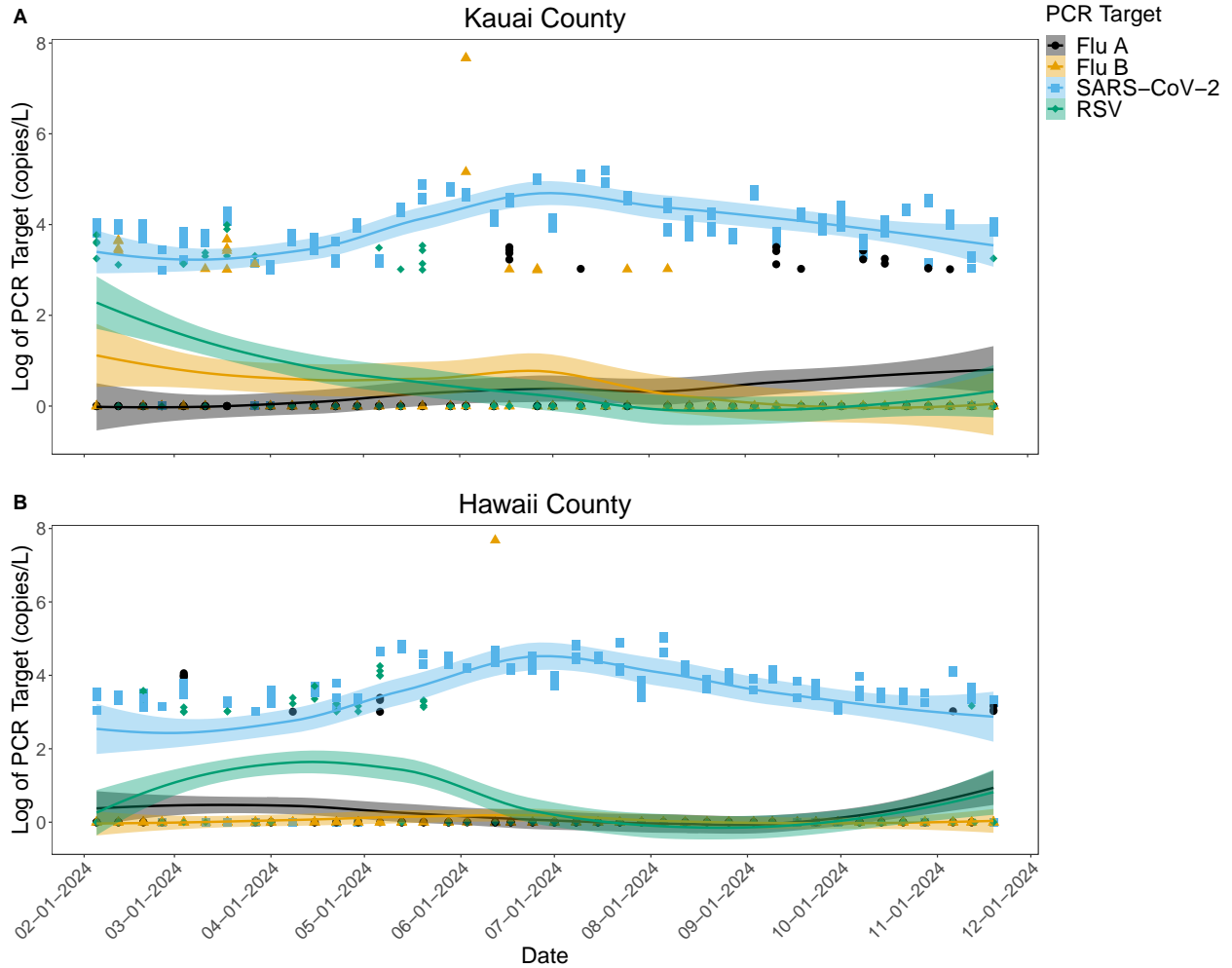
## 5 Hawaii State Laboratories Division

The Hawaii State Laboratories Division (SLD) is developing local wastewater testing capabilities. All participating WWTP collect sewage samples once weekly which are sent to the state laboratory for processing. Methods for processing includes concentration, DNA/RNA extraction, and pathogen quantification with digital PCR (dPCR). These methodologies differ from contracted labs from NWSS (Verily), and WastewaterSCAN. The Hawaii SLD utilizes the liquid fraction of raw influent for processing unlike WastewaterSCAN which uses sludge. Currently, dPCR assays are targeting respiratory pathogens specifically SARS-CoV-2, Flu A, Flu B, RSV, NoV GI and NoV GII. Still, methods are in continual development such as improving the recovery of targeted pathogens and expanding dPCR assays. For this report, data is included from Kauai County and Hawaii County. Concentrations of each target quantified by the Hawaii SLD are reported as log-transformed copies per L of raw sewage.

### Metadata for participating WWTP by county

County	Number of WWTP	Total Population Served
Kauai	1	10,000
Hawaii	1	32,604

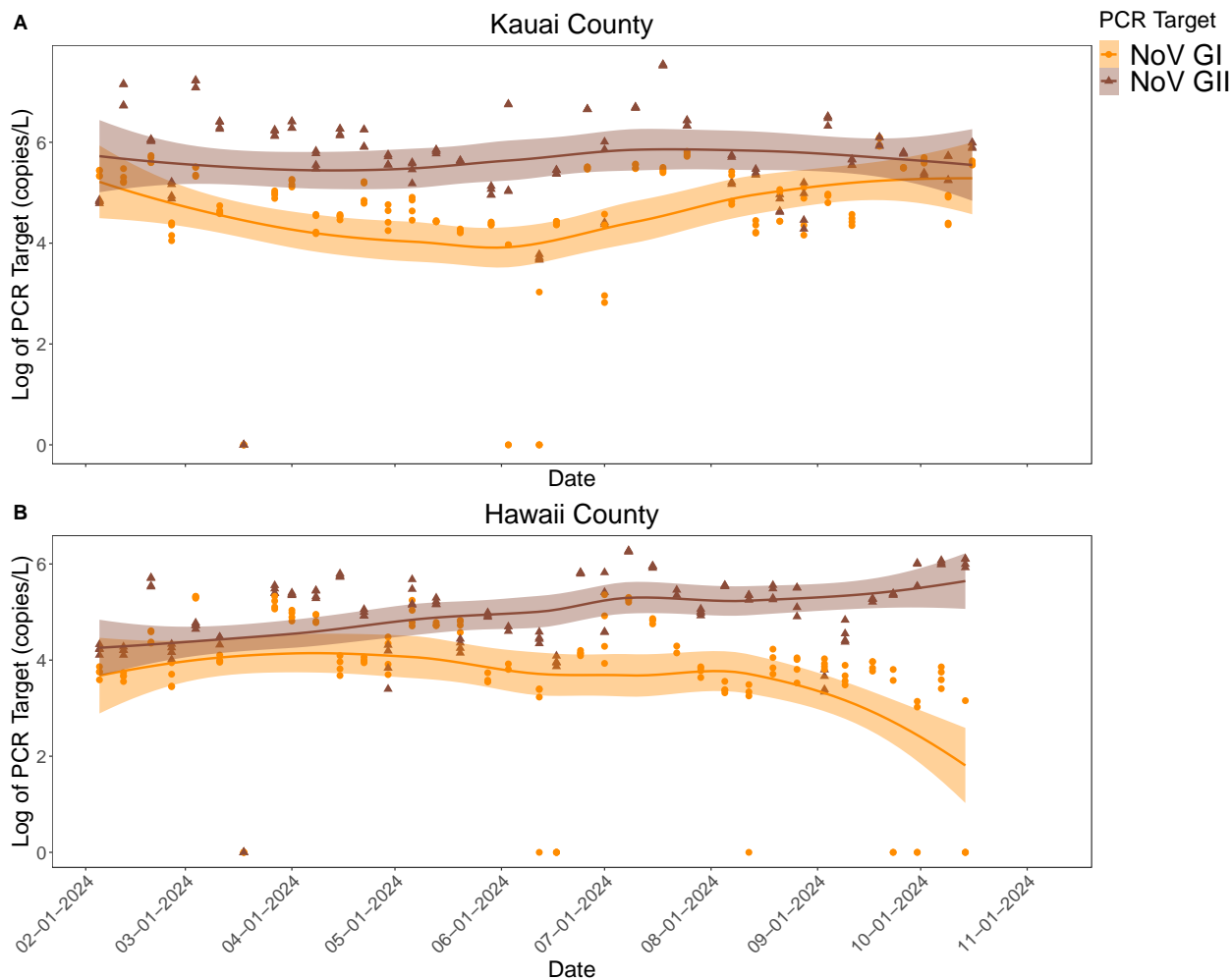
## 5.1 Hawaii SLD: Respiratory Pathogens Wastewater Surveillance Data



**Figure 11.** Log transformed average concentrations of Flu A, Flu B, SARS-CoV-2, and Respiratory Syncytial Virus (RSV) in sewage from (A) Kauai County and (B) Hawaii County WWTP over time from 02/01/2024 to 11/20/2024. Regression line created with a prediction interval from a locally weighted (LOESS) regression. Shaded region represents 95% confidence interval. Values below the limit of detection (LOD) are reported as 0 copies/L.

**Notes:** Across both counties, concentrations of SARS-CoV-2 in sewage is relatively stable. Flu A, Flu B, and RSV wastewater concentrations in both counties are frequently below the LOD.

## 5.2 Hawaii SLD: Gastrointestinal Pathogens Wastewater Surveillance Data



**Figure 12.** Log transformed average concentrations of two genotypes of Norovirus (NoV), NoV GI and NoV GII, in sewage from (A) Kauai County and (B) Hawaii County WWTP over time from 02/01/2024 to 11/06/2024. Regression line created with a prediction interval from a locally weighted (LOESS) regression. Shaded region represents 95% confidence interval. Values below the limit of detection (LOD) are reported as 0 copies/L.

**Notes:** NoV GI and NoV GII are found at consistently high concentrations compared to other pathogens since those infected primarily shed NoV in feces. Overall NoV are relatively stable across both counties with NoV GII consistently found in higher concentrations. Kauai's NoV GII outbreak associated with the Napali Coast State Wilderness Park from August through September 2024 was not detected via wastewater surveillance. This is likely due to the single participating WWTP collection site on Kauai not being a likely catchment area for local residents or visitors involved in the outbreak.

## 6 Resources

- National Wastewater Surveillance System (NWSS): <https://www.cdc.gov/nwss>
  - <https://www.cdc.gov/healthywater/surveillance/wastewater-surveillance/wastewater-surveillance.html>
  - How it works: <https://www.cdc.gov/healthywater/surveillance/wastewater-surveillance/resources/how-wws-works.html>
  - Data Reporting: <https://www.cdc.gov/healthywater/surveillance/wastewater-surveillance/data-reporting-analytics.html>
  - Data: <https://covid.cdc.gov/covid-data-tracker/#wastewater-surveillance>
  - <https://covid.cdc.gov/respiratory-viruses/data/index.html#respiratory-dashboard-module>
  - Testing Methods:  
<https://www.cdc.gov/healthywater/surveillance/wastewater-surveillance/testing-methods.html>
- Verily: <https://verily.com>
  - Public health: <https://verily.com/solutions/public-health/wastewater>
  - WastewaterSCAN: <https://publichealth.verily.com/?d=3m&v=SARS-CoV-2>
- WastewaterSCAN: <https://wastewaterscan.org/>
  - Data: <https://data.wastewaterscan.org/>
  - Methodology and Protocol: <https://data.wastewaterscan.org/about>
  - <https://www.protocols.io/view/high-throughput-pre-analytical-processing-of-waste-kxygxpod4l8j/v2>
  - <https://www.protocols.io/view/high-throughput-rna-extraction-and-pcr-inhibitor-r-81wgb72bovpk/v2>
  - <https://www.protocols.io/view/high-throughput-sars-cov-2-pmmov-and-bcov-quantifi-e6nvw5orwvmk/v5>
  - <https://www.protocols.io/view/quantification-of-various-sars-cov-2-variant-mutat-14egnzzrzg5d/v11>
- SARS-CoV-2 Variant Classifications:
  - <https://www.cdc.gov/coronavirus/2019-ncov/variants/variant-classifications.html#:~:text=SARS%2DCoV%2D2%20has%20many,contain%20one%20or%20more%20mutations.>
- Information on other pathogens surveyed by wastewater:
  - Influenza (Flu A and Flu B): <https://www.cdc.gov/flu/about/index.html>
  - <https://www.cdc.gov/flu/about/viruses/types.htm>
  - H3 and H5: <https://www.cdc.gov/bird-flu/about/index.html>
  - <https://www.cdc.gov/mmwr/volumes/73/wr/mm7337a1.htm>
  - RSV: <https://www.cdc.gov/rsv/index.html>
  - <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3461981/>
  - Norovirus: <https://www.cdc.gov/hai/organisms/norovirus.html>
  - <https://www.cdc.gov/norovirus/lab/virus-classification.html>
  - <https://journals.asm.org/doi/10.1128/jvi.01364-10>

- MPOX and NVO: <https://www.cdc.gov/poxvirus/mpox/symptoms/index.html>
  - <https://www.cdc.gov/poxvirus/mpox/index.html>
  - *C. auris*: <https://www.cdc.gov/fungal/candida-auris/index.html>
  - <https://www.cdc.gov/drugresistance/pdf/threats-report/candida-auris-508.pdf>
  - <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7211321/>
  - <https://www.ncbi.nlm.nih.gov/books/NBK563297/>
- More about wastewater surveillance for SARS-CoV-2 and other pathogens:
    - <https://www.sciencedirect.com/science/article/pii/S2590049822000078>
    - <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8416286/>
    - <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7583624/>
    - <https://www.nature.com/articles/s41586-022-04980-y>
    - <https://www.nature.com/articles/s41586-022-05049-6>
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    - <https://pubmed.ncbi.nlm.nih.gov/34153546/>
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    - <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8769679/>
    - <https://pubs.acs.org/doi/10.1021/acs.estlett.1c00963>
    - <https://pubs.acs.org/doi/10.1021/acs.est.2c07763>