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Correlation of wastewater surveillance data with traditional influenza surveillance measures in Cook County, Illinois, October 2022–April 2023

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Abstract

Influenza is a respiratory illness that can result in serious outcomes, particularly among persons who are immunocompromised, aged <5 years or aged >65 years. Traditional influenza surveillance approaches rely upon syndromic surveillance of emergency departments and public health reporting from clinicians and laboratories. Wastewater surveillance infrastructure developed to monitor SARS-CoV-2 is being used for influenza surveillance in the Chicago area. The goal was to evaluate timeliness and correlations between influenza virus detected through wastewater surveillance and traditional influenza surveillance measures to assess utility of wastewater surveillance for influenza at the county level. Specifically, we measured correlations between influenza virus gene copies in wastewater samples and 1) the number of intensive care unit admissions associated with a diagnosis of influenza, 2) the percentage emergency

[2]Note: Visits may represent individual patients more than once.

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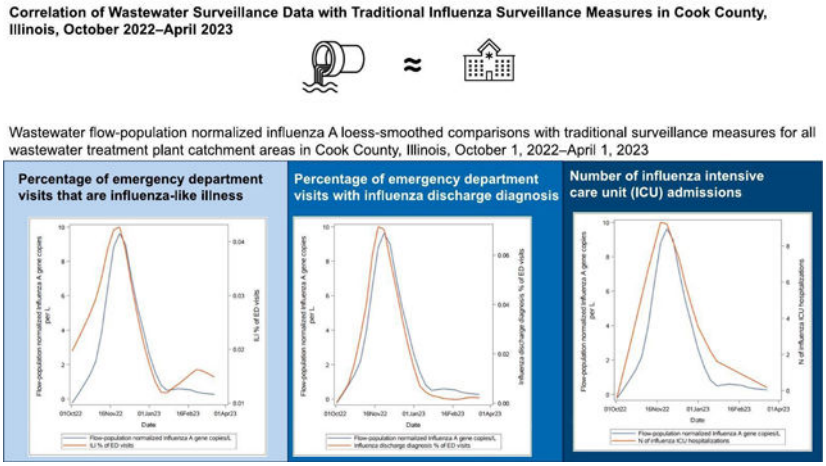
department (ED) visits for influenza-like-illness, and 3) the percentage of ED visits with influenza diagnosis at discharge[2] in Cook County. Influenza concentrations in wastewater were strongly correlated with traditional influenza surveillance measures, particularly for catchment areas serving >100,000 residents. Wastewater indicators lagged traditional influenza surveillance measures by approximately one week when analyzed in cross-correlations. Although wastewater data lagged traditional influenza surveillance measures in this analysis, it can serve as a useful surveillance tool as a complement to syndromic surveillance; it is a form of influenza surveillance that does not rely on healthcare-seeking behavior or reporting by healthcare providers.

Graphical Abstract



Keywords

Influenza; Wastewater-based epidemiology; Wastewater surveillance

1. Introduction

Influenza is a common and potentially serious respiratory illness. Certain groups, including persons aged >65 years, immunocompromised persons, and children aged <5 years are at increased risk of severe illness (Grohskopf et al., 2023). Before 2020, influenza had traditionally been monitored in Illinois through different indicators, including syndromic surveillance of influenza-like-illness (ILI) in emergency department (ED) visits and mandatory reporting of severe outcomes (e.g., intensive care unit [ICU] admissions). Wastewater surveillance approaches developed in response to the COVID-19 pandemic have been adapted for community influenza surveillance in Cook County, Illinois, to monitor influenza virus at a population level (Kirby et al., 2021). Utility of wastewater surveillance varies for each pathogen of interest because of differences in how persons shed different viruses and laboratory methods used to detect each individual pathogen (Zhang et al., 2021). This analysis evaluates the timeliness and correlations between wastewater concentration of influenza virus and traditional influenza surveillance measures, including both influenza-associated intensive care unit admissions and syndromic surveillance, to examine the application of wastewater surveillance to influenza surveillance in Cook

County, IL. The goal was to estimate timeliness and correlation between wastewater surveillance and traditional influenza surveillance measures on a county level to determine utility of wastewater surveillance in estimating influenza disease burden at a population level. We hypothesize that wastewater concentration of influenza virus will be strongly correlated with traditional influenza surveillance measures.

2. Material and methods

In late 2020, the Chicago Department of Public Health, Cook County Department of Public Health, and Illinois Department of Public Health, began collecting wastewater samples from wastewater treatment facilities and neighborhood sewersheds for SARS-CoV-2 surveillance. SARS-CoV-2 viral RNA in samples were quantified and sequenced to monitor viral concentration levels and emerging SARS-CoV-2 variants of concern. During October 2022–April 2023, influent samples from eight wastewater treatment facilities covering the City of Chicago and adjacent Cook County suburbs were collected and tested for influenza A and B virus RNA. The largest wastewater treatment plant was sampled twice weekly and all other wastewater treatment plants were sampled three times weekly. Liquid composite influent wastewater samples were collected and concentrated using Ceres Nanotrap Microbiome A particles, and RNA was extracted using the MagMax Viral/Pathogen Nucleic Acid Isolation kit (Karthikeyan et al., 2021). Influenza A and influenza B were quantified with the GT Molecular GT-Digital Influenza and SARS-CoV-2 Wastewater Surveillance Multiplex Assay Kit for the QIAcuity Digital PCR System, which identifies the M1 gene of influenza A and the NS2 gene of influenza B.

This analysis calculated correlations between wastewater influenza A concentration[3] and three traditional influenza surveillance measures: (A) number of ICU admissions associated with influenza reported in Illinois' National Electronic Disease Surveillance System[4]; (B) percentage of ED visits for respiratory illness that included fever and cough or sore throat, also referred to as influenza-like illness (ILI)[5]; and (C) percentage of ED visits with an influenza diagnosis at discharge among Cook County residents reported by Illinois acute-care hospitals in the Electronic Surveillance System for the Early Notification of Community-Based Epidemics during October 1, 2022–April 15, 2023.[6] Wastewater sample collection and processing methods were described previously (Feng et al., 2023; Owen et al., 2022). Given potential stochastic imprecision in wastewater measurements and potential spatial error, the three traditional influenza surveillance measures were presented at the county level and stratified into one of eight wastewater treatment plant (WWTP) catchment areas based on resident postal code. To address potential overlap in wastewater treatment plant boundaries, they were geocoded and assigned to zip code by percentage coverage

[3]The focus was on the correlation between influenza A concentration in wastewater and influenza surveillance measures because levels of influenza B were not detectable in wastewater during the study period.

[4]ICU hospitalizations with a diagnosis of influenza included residents of Cook County who had a hospital admission during 2022–2023 and had a positive influenza test within two weeks before or during hospitalization.

[5]Influenza-like illness (ILI) is defined as fever ≥100 °F with a cough or sore throat. The number of Electronic Surveillance System for the Early Notification of Community-Based Epidemics (ESSENCE) emergency department (ED) visits matching this influenza-like illness definition were divided by the total number of ED visits in ESSENCE for each catchment area.

[6]The percentage of ED visits with influenza diagnosis at discharge was based on the number of visits with the following diagnosis codes at discharge divided by all ED visits in ESSENCE by catchment area: ICD-9-CM: 487.0, 487.1, 487.8, 488.01, 488.09, 488.11, 488.19, 488.81, 488.89; ICD-10-CM: J09, J10, J11; and SNOMED CT: 442696006, 442438000, 6142004, and 195878008.

of each treatment plant in the zip code. Wastewater gene copy concentration levels were normalized by multiplying by flow rate at corresponding sample collection date and dividing by the population in the WWTP catchment area. This method accounts for changes in daily wastewater contributions. Sensitivity analysis was conducted applying normalization by dividing influenza gene copies per liter by pepper mild mottle virus (PMMoV) gene copies per liter at the corresponding sample collection date (Rainey et al., 2023). This method uses a normalization target that can be measured in wastewater to estimate human fecal concentration to account for viral losses and recovery in sewage system and laboratory processes. Wastewater and traditional surveillance data was aggregated by MMWR week to account for day-to-day variability due to random noise in wastewater data and day of the week effects in clinical data collection. Additionally, sensitivity analyses using a 7 day rolling average for traditional surveillance outcomes and analyses interpolating to daily metrics were also conducted to test if weekly aggregation impacted results. The time lag between wastewater and traditional surveillance measures was estimated using cross-correlations. Nonlinear trends between influenza A levels in wastewater and the clinical metrics were visualized using locally weighted regression (LOESS) (PROC SGPLOT LOESS statement in SAS®, version 9.4 [SAS Institute, Inc., Cary, North Carolina]). Cross-correlations were calculated for each surveillance measure with reporting lags from −24 weeks to 24 weeks and evaluated using Spearman's correlation coefficients. All statistical analyses were conducted in SAS 9.4 and R version 4.2.2. This activity was reviewed by CDC and conducted consistent with applicable federal law and CDC policy.[7]

3. Results

Among 574 samples analyzed from eight wastewater treatment plants during October 2022–April 2023, a total of 344 samples had quantifiable influenza A RNA, for which the median viral RNA level was 12,525 gene copies/L (interquartile range 4200–40,706.25).

Timing and correlation between wastewater flow-population normalized influenza A compared with traditional influenza surveillance measures in Cook County during October 1, 2022–April 1, 2023, are presented in Fig. 1A–C. Wastewater flow-population normalized influenza A peaked in late November and early December 2022. Cross-correlation trends showed that wastewater flow-population normalized influenza A gene copies lagged one week behind all traditional influenza surveillance indicators (Fig. 2A–C) (maximum cross correlation coefficients for % ILI syndrome in ED visits: 0.89; % ILI discharge diagnosis in ED visits: 0.95; and influenza diagnoses in ICU admissions: 0.96). All results applying wastewater normalization by flow-population were consistent in comparisons applying normalization by PMMoV. These results were consistent in sensitivity analyses using a 7-day moving average and when analyzing data on the daily level using interpolation, with lags ranging from 2 to 4 days for traditional surveillance measures.

Positive correlations were observed between wastewater flow-population normalized influenza A and traditional influenza surveillance measures in Cook County. County-level correlations were greatest for wastewater and syndromic surveillance of ED visits with

[7]45 C.F.R. part 46.102(l)(2), 21 C.F.R. part 56; 42 U.S.C. Sect. 241(d); 5 U.S. C.0 Sect. 552a; 44 U.S.C. Sect. 3501 et seq.

a discharge diagnosis of influenza (wastewater flow-population normalized influenza A: $\rho = 0.69$, $p < 0.0001$ and wastewater PMMoV normalized influenza A: $\rho = 0.74$, $p < 0.0001$). Correlation coefficients were lowest for wastewater and total percentage of ILI visits (wastewater flow-population normalized influenza A: $\rho = 0.44$, $p < 0.0001$ and wastewater PMMoV normalized influenza A: $\rho = 0.43$, $p < 0.0001$) and ICU admissions for influenza (wastewater flow-population normalized influenza A: $\rho = 0.51$, $p < 0.0001$ and wastewater PMMoV normalized influenza A: $\rho = 0.53$, $p < 0.0001$).

Although significant correlations were found between wastewater flow-population normalized influenza A and all three traditional surveillance indicators, influenza detection was more pronounced and earlier with traditional influenza surveillance measures than influenza A RNA concentration in wastewater. These findings were consistent across catchment areas. Correlations were strongest for the percentage of influenza discharge diagnoses in ED visits, compared with other traditional surveillance measures (Spearman's correlation coefficients ranging from 0.50 to 0.89, $p \leq 0.01$ for all treatment plants). Dis-aggregated analyses for each WWTP within Cook County (Table 1) show the strongest correlations for percentage of ILI in ED visits (r range = 0.56–0.72, $p < 0.01$), percentage of influenza discharge diagnoses in ED visits (r range = 0.50–0.89, $p \leq 0.01$) and number of influenza diagnoses among ICU admissions (r range = 0.64–0.86, $p < 0.01$) were found at larger catchment areas (WWTPs A, B, C serving populations of 1.1–2.3 million residents). The weakest correlation was in catchment area G, which had the smallest catchment area population in Cook County ($r = 0.16$, $p = 0.45$), serving a population of approximately 13,000 residents.

4. Discussion

Wastewater surveillance for Influenza was strongly correlated with influenza activity across multiple treatment plants with large population catchment areas using concentrations of influenza viral genes in wastewater. Timing of the wastewater concentration peak indicated that wastewater samples might lag traditional influenza surveillance, such as ILI visits. The strongest correlations were observed when comparing wastewater concentrations with percentage of ED visits with a discharge diagnosis of influenza. Using the discharge diagnosis excluded ILI cases that might not have been attributable to influenza. However, it might have excluded other patients who did have influenza but did not have a discharge diagnosis or did not fully meet the syndromic definition for ILI (e.g., if only one symptom is present).

Our results are consistent with other recent studies that analyzed the correlation between wastewater and influenza surveillance measures. The highest cross-correlation we detected was a one-week lag, while other studies demonstrated that wastewater was a leading indicator. However, we also observed one-week or zero-week leads in our study period, which are biologically plausible. Lead times may not be detected with wastewater for our population due to the system's resolution and the type of metrics we used. Differences in results from other studies may be due to differences in the surveillance measures (i.e., test positivity rates) being compared to wastewater, wastewater sampling frequency, and variations of analyses conducted (cross-correlations compared to differences in detection

dates). Thus, different methods to determine lead time could impact conclusions across wastewater systems. This highlights the need for more uniformity in approaches to assessing lead and lag times for wastewater surveillance compared to traditional surveillance approaches.

The findings in this study are subject to multiple limitations. First, comparisons with surveillance measures are based on reported residence of ICU and syndromic surveillance cases in the wastewater catchment area. The wastewater catchment area might not exactly match the surveilled population, which might inflate or dilute viral concentration levels and limit the ability to make comparisons of wastewater location and location of residence. Even when the population contributing to wastewater remains the same, the locations where virus is detected and where cases are attributed might be different because of individual mobility. Second, influenza virus infections generally result in more severe illness in young and old populations (Grohskopf et al., 2023). The populations surveilled in this analysis are different because wastewater captures everyone using the sewer system. Third, influenza type in Illinois ED data did not differentiate between influenza A or influenza B and might have overestimated influenza A cases as influenza B cases were not detectable in wastewater but were detected in traditional surveillance during this period. However, 98.6 % of positive influenza PCR tests collected by five clinical laboratories and two commercial pharmacies serving Chicago during the study period were identified as influenza A.

5. Conclusions

Wastewater surveillance of influenza can serve as a complement to traditional influenza surveillance because it can contribute community influenza activity that is not captured in syndromic surveillance or through provider reporting of severe influenza manifestations. This analysis showed that the association between wastewater concentrations and traditional influenza surveillance measures were consistent over time, and statistically significant correlations were found between wastewater concentrations and multiple clinical measures of influenza burden. However, influenza concentration in wastewater was not shown to precede traditional surveillance measures, as has been reported for COVID-19 in certain locations (Peccia et al., 2020; Randazzo et al., 2020). Therefore, wastewater surveillance as a signal for increases in influenza burden may be more informative when clinical data are limited. Development of a wastewater surveillance system requires a large initial investment, but adding targets to an existing wastewater surveillance system involves a limited incremental expense, particularly for multiplex assays that can be utilized for multiple targets, such as respiratory viruses. Wastewater surveillance for influenza might be most useful in identifying influenza trends in jurisdictions lacking emergency department or ICU data as a supplement to traditional influenza surveillance or as at-home testing becomes available and fewer cases are detected in clinical settings (U.S. Food and Drug Administration, 2023).

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Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Aaron Packman reports that financial support was provided by Chicago Department of Public Health. Rachel Poretsky reports that financial support was provided by Chicago Department of Public Health. Melissa Pierce reports that financial support was provided by Chicago Department of Public Health. Katelyn Leisman reports that financial support was provided by Chicago Department of Public Health. Emily AG Faherty reports that administrative support was provided by Chicago Department of Public Health. Alyse Kittner reports that financial support was provided by the Centers for Disease Control and Prevention. Deniz Yuce reports that financial support was provided by the Centers for Disease Control and Prevention. Colin Korban reports that financial support was provided by the Centers for Disease Control and Prevention. Rishi Kowalski reports that travel was provided by the Council of State and Territorial Epidemiologists. Alyse Kittner reports that travel was provided by Water Environment Federation. Rachel Poretsky reports that equipment, drugs, or supplies was provided by the National Institutes of Health. Stephanie Gretsch reports that financial support was provided by the Centers for Disease Control and Prevention. Aaron Packman reports that financial support was provided by Illinois Department of Public Health. Katelyn Leisman reports that financial support was provided by Illinois Department of Public Health. Melissa Pierce reports that financial support was provided by Illinois Department of Public Health. Aaron Packman reports a relationship with Integrated Bioscience and Built Environment Consortium that includes: board membership.

Data availability

The authors do not have permission to share data.

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HIGHLIGHTS

- Wastewater complemented traditional influenza surveillance at the county level.
- Wastewater concentrations were correlated with traditional surveillance measures.
- Wastewater influenza concentrations reflect community influenza activity.
- Wastewater does not vary by health-seeking behavior or public health reporting.

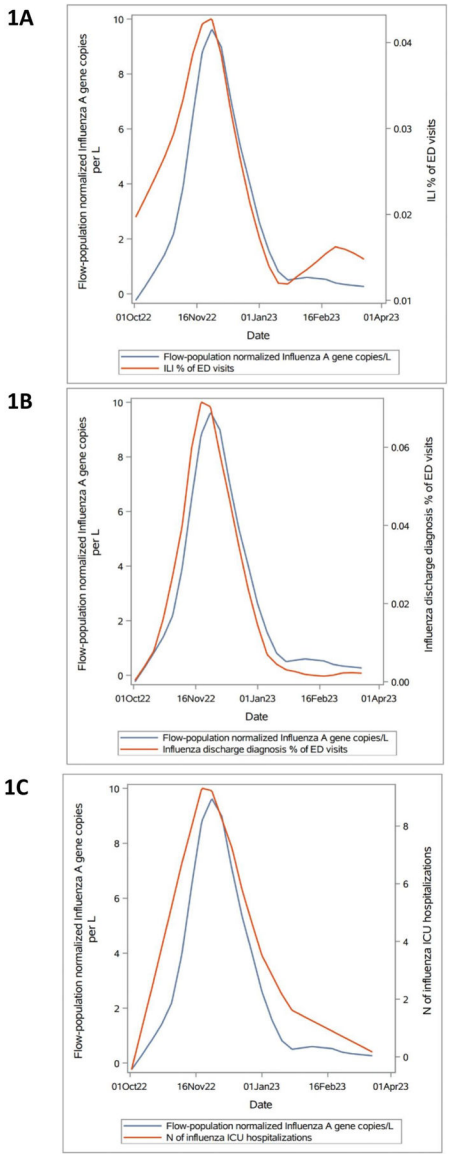

Fig. 1.

Wastewater flow-population normalized influenza a loess-smoothed comparisons with: 1a) % influenza-like illness (ili) in total emergency department (ed) visits; 1b) % emergency department visits with influenza discharge diagnosis; and 1c) number of influenza intensive care unit (icu) admissions for all wastewater treatment plant catchment areas in Cook County, Illinois, October 1, 2022–April 15, 2023.

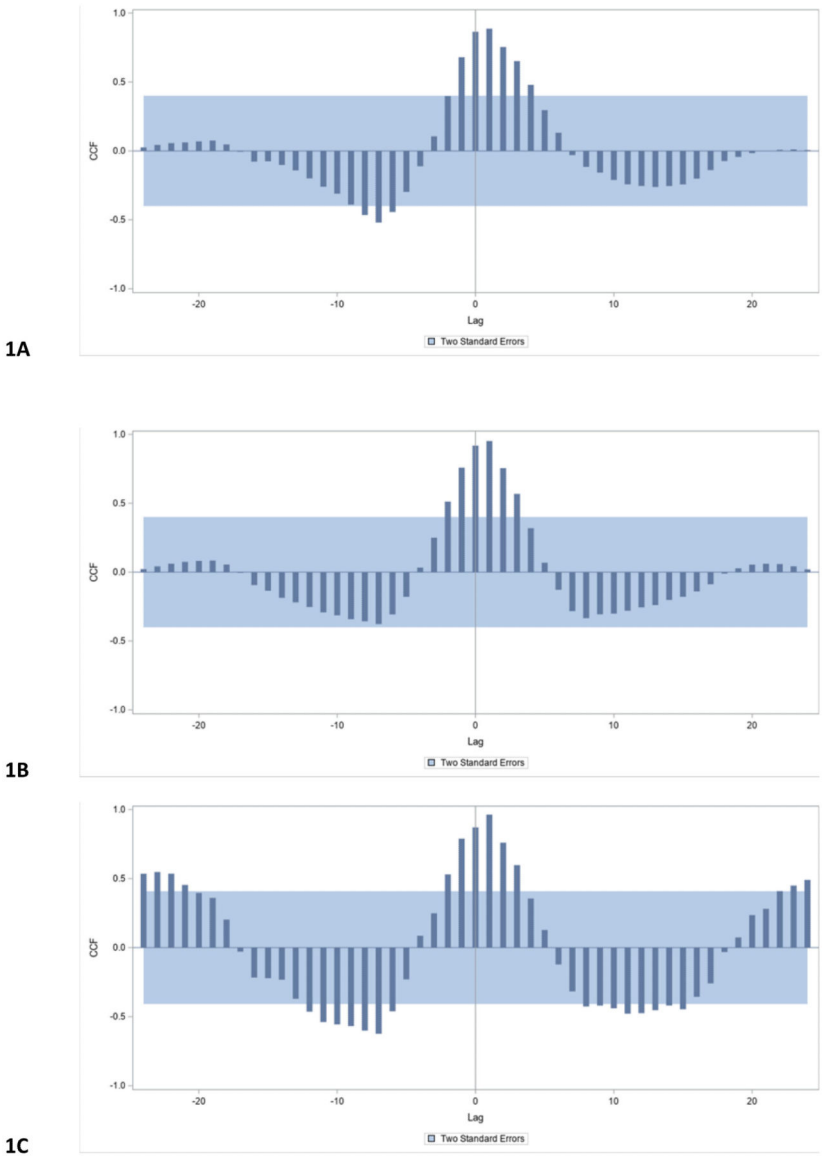

Fig. 2.

Cross-correlation values by week for wastewater flow-population normalized influenza A rate compared with: 2A) % influenza-like illness in total emergency department visits; 2B) % emergency department visits with influenza discharge diagnosis; and 2C) number of influenza intensive care unit admissions for all wastewater treatment plant catchment areas in Cook County, Illinois, October 1, 2022–April 15, 2023.

Table 1

Correlation between flow-population normalized wastewater concentration[a] and traditional influenza surveillance indicators[b] by wastewater treatment plan catchment areas in Cook County, Illinois, October 1, 2022–April 15, 2023.

Wastewater treatment plant catchment area	Population served	% of emergency department visits for ILI[c]		% of emergency department visits with influenza discharge diagnoses[d]		No. of influenza ICU admissions	
		r[e]	*p*-Value	r	p-Value	r	p-Value
A[f]	1,263,110	0.72	<0.0001	0.89	<0.0001	0.86	<0.0001
B[f,g]	2,255,473	0.70	<0.0001	0.81	<0.0001	0.87	<0.0001
C[f]	1,134,897	0.56	0.0034	0.50	0.0108	0.64	0.0072
D	217,106	0.72	<0.0001	0.89	<0.0001	0.39	0.4411
E	110,394	0.71	0.0001	0.83	<0.0001	–	–
F	270,647	0.66	0.0003	0.88	<0.0001	−0.22	0.7177
G	13,098	0.16	0.4541	0.63	0.0007	–	–
Cook County Total	5,264,765	0.44	<0.0001	0.69	<0.0001	0.51	<0.0001

[a]Flow-population normalization estimates viral concentrations by daily wastewater flow and by the number of persons served by the wastewater treatment plant to account for changes in wastewater contributions and population served per day.

[b]ICU hospitalizations with a diagnosis of influenza included residents of Cook County who had a hospital admission during 2022–2023 who had a positive influenza test within two weeks before or during hospitalization.

[c]Influenza-like illness (ILI) is defined as fever ≥100 °F with a cough and/or sore throat. The number of Electronic Surveillance System for the Early Notification of Community-Based Epidemics (ESSENCE) emergency department (ED) visits matching this influenza-like illness definition were divided by the total number of ED visits in ESSENCE for each catchment area.

[d]The percentage of ED visits with influenza diagnosis at discharge was based on the number of visits with the following diagnosis codes at discharge divided by all ED visits in ESSENCE by catchment area: ICD-9-CM: 487.0, 487.1, 487.8, 488.01, 488.09, 488.11, 488.19, 488.81, 488.89; ICD-10-CM: J09, J10, J11; and SNOMED CT: 442696006, 442438000, 6142004, and 195878008.

[e]r-denotes Spearman's correlation coefficient.

[f]Wastewater treatment plant serves the city of Chicago.

[g]Data from two wastewater treatment plant sampling sites serving the same catchment area were combined.