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Wastewater-based monitoring could help guide responses to the USA opioid epidemic

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The successful use of wastewater-based data during the COVID-19 pandemic has led to the creation of the National Wastewater Surveillance System in the USA for pathogen monitoring. Now a complementary system is needed for help tackling the opioid epidemic.

In 2021, the Centers for Disease Control and Prevention (CDC) reported annual deaths from drug-involved overdoses in the United States exceeded 100,000 people, with opioids primarily responsible for 75% of overdoses[1]. With opioid overdose deaths having accelerated during the COVID-19 pandemic, better data are urgently needed to illuminate the dynamic shifts in drug use that are occurring. Wastewater-based epidemiology has played a significant role in helping officials monitor and respond to the COVID-19 pandemic[2]. This innovative approach to public health surveillance can also be harnessed for more timely monitoring of the opioid epidemic.

Around the world, wastewater-based epidemiology has become a valuable public health tool to identify the emergence and progression of COVID-19 outbreaks. The CDC has partnered with the US Department of Health and Human Services and other agencies to establish a National Wastewater Surveillance System (NWSS). The current system, which covers 46 states, five cities and two territories (more than 133 million people), is oriented to addressing the COVID-19 pandemic, with an eye towards future monitoring of foodborne illnesses and antimicrobial resistance[3].

We believe that the United States should develop a similar system to monitor the use of opioids and other drugs. Specifically, there is a need for support from federal agencies to boost the analytic capabilities of testing labs across the county for wastewater monitoring, conduct inter-laboratory validation studies to ensure nationwide robustness, coordinate with state and tribal health agencies to facilitate widespread sampling that is conducted in an ethical manner, and develop standardized reporting procedures and clear messaging around the results. The CDC would be the most appropriate agency to lead this effort, given their leadership with NWSS. A 2023 National Academies report on wastewater-based infectious disease surveillance stated that[4]: "[w]hen evaluating potential targets for future wastewater surveillance, CDC should consider three criteria: (1) public health significance of the threat, (2) analytical feasibility for wastewater surveillance, and (3) usefulness of community-level wastewater surveillance data to inform public health action." While this was written with infectious disease as the focus, we believe this sentiment and these three criteria perfectly match with using wastewater for opioid monitoring.

Wastewater is essentially a pooled urine and faeces sample of a community that includes biomarkers of both biological and chemical exposures. A national wastewater surveillance system to monitor opioids and other emerging illicit drugs such as benzodiazepines could help public health and safety officials anticipate new drug outbreaks and respond more quickly to protect the health of US citizens.

Although US government and health officials have data on opioid prescribing practices, hospital admissions, drugs seizures, surveys, and arrests, the release of these data usually lags well behind trends in opioid use because it takes time to collect, structure, analyse, and report the data. Further, people often do not know which opioids or other drugs they are consuming, and so cannot accurately report such on the self-reported surveys that the federal government relies on to understand drug use trends, the populations affected, and the need for treatment services. Wastewater data, by contrast, provide more granular, drug specific, near-real-time information on patterns of opioid and other drug use.

Technical considerations

Wastewater-based epidemiology has been used for over a decade in Australia and Europe, and to a lesser extent North America and Asia, to monitor population trends in licit and illicit drug use. Wastewater evidence of a five-fold increase in methamphetamine use in Australia from 2009 to 2015 led the Australian Government to establish a National Wastewater Drug Monitoring Program. Subsequent monitoring of fentanyl observed a higher baseline use in rural areas, and a nearly 150% increase in consumption between 2016 and 2018.

Wastewater-based epidemiology can detect community use of natural and synthetic opioids including fentanyl and some of its analogues. Detecting fentanyl and its analogues can be more analytically challenging given that these compounds are highly potent, with typical doses in micrograms instead of milligrams. Such potency leads to levels of less than 10 parts per trillion in wastewater – two to three orders of magnitude below that of many prescription opioids[5]. Indeed, trace levels of fentanyl in wastewater were not quantifiable less than a decade ago. However, recent advancements in instrumentation and methodology now allows for detection limits in the picogram per litre range and produce a quantifiable measurement of fentanyl (and its unique metabolite, norfentanyl) in wastewater that is robust and can be used to reliably estimate drug use[5]. Further, guidance from forensic laboratories, informed by data on the causes of deaths and hospital admissions due to drug overdoses, can improve detection of emerging fentanyl analogues in wastewater and increase the likelihood of identifying regional trends earlier in wastewater. In other words, wastewater surveillance to identify analogues as a 'first line of defence' is not currently practical but could become so with additional research, information sharing, and coordination.

Table 1 | Major opioid metabolites and potential wastewater-based epidemiology biomarkers[14]

Opioid drug	Opiate category	Active metabolites identical to pharmaceutical opioids	Active metabolites distinct from pharmaceutical opioids	Possible wastewater-based epidemiology biomarkers	Analytical methods for detection in wastewater	Data limitations and areas for further research
Morphine	Natural opiate	Hydromorphone	Morphine-3-G glucuronide	Morphine	✓	Combined signal from several sources
Codeine	Natural opiate	Hydrocodone	Norcodeine	Codeine, norcodeine	✓	No limitations
Oxycodone	Semi-synthetic opioid	Oxymorphone	Noroxycodone	Oxycodone, noroxycodone	✓	No limitations
Hydrocodone	Semi-synthetic opioid	Hydromorphone	Norhydrocodone	Hydrocodone, norhydrocodone	✓	No limitations
Oxymorphone	Semi-synthetic opioid	None	6-Hydroxy-oxymorphone	Oxymorphone	✓	No limitations
Meperidine	Synthetic opioid	None	Unknown	Meperidine, normeperidine	✓	No limitations
Tramadol	Synthetic opioid	None	Desmetramadol	Tramadol, desmetramadol	✓	No limitations
Fentanyl	Synthetic opioid	None	None	Fentanyl, norfentanyl	✓	Best practices absolutely necessary with standardized protocols to achieve necessary sensitivity
Fentanyl analogs	Synthetic opioid	Pharmacokinetics are mostly unknown	Few are known, mostly unknown	Parent drugs	Currently limited to few analogues and new analogues are produced regularly	Rare, low levels, constantly changing More study needed and may only be at a detection level with high-resolution mass spectrometry
Buprenorphine	Synthetic opioid	None	Norbuprenorphine	Buprenorphine, Norbuprenorphine	✓	No limitations
Methadone	Synthetic opioid	None	EDDP (2-Ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine)	EDDP (2-Ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine)	✓	No limitations
Heroin	Synthetic opioid	Morphine	6 Monoacetylmorphine	6 Monoacetylmorphine	✓	Absolute consumption not possible but trends within a catchment possible

Suitable wastewater biomarkers should be specific to human metabolism, excreted mainly via urine, measurable in wastewater, and stable in wastewater and the sewer system[6]. Selected opioids and their human-specific metabolites are stable biomarkers in wastewater (Table 1). However, certain opioids metabolize to other opioids or produce identical metabolites, hence complicating interpretation (Table 1). For example, heroin's primary metabolite—morphine—is also used pharmaceutically, and codeine contained in over-the-counter medications also metabolises into morphine in wastewater. While heroin has a unique metabolite, 6-monoacetylmorphine (6-MAM), it is not particularly stable in wastewater, and individual chemical and physical characteristics within a catchment basin (that is, the area served by a centralized wastewater treatment plant) may influence the levels of this metabolite. Despite these challenges, 6-MAM has the potential to reveal informative trends within a catchment. While wastewater testing methods alone cannot distinguish illicit from prescription use of fentanyl, the total signal may provide the trends and scale of illicit use when estimates of prescription data are removed.

Ethical considerations

The foundational idea of monitoring wastewater to assess community drug use emerged when the US Environmental Protection Agency, and the Office of National Drug Control Policy conducted one of the first pilot studies of this innovative approach to public health surveillance a decade and a half ago. A wastewater sample contains the information of thousands to millions of people, which means no individuals can be identified. However, the US federal government has been hesitant to pursue wastewater monitoring for opioids because of concerns around community stigmatization[7]. Further, with longstanding mistrust between public health and law enforcement officials in addressing substance use[8], the public may be concerned that a publicly available NWSS-type system could be used punitively by public safety agencies. As the report by the National Academies suggests, a strong firewall should be maintained that precludes use of data by law enforcement[4].

Despite these fears, experience with wastewater-based studies of illicit drug use in Europe and Australia over the past decade and a half has not produced any misuses of wastewater data by law enforcement,

possibly due to the highly available and public nature of these data. Reports published by the EMCDDA and the Australian National Wastewater Drug Monitoring Program on trends in the population use of different types of illicit drugs have informed the development of policy responses to the harms caused by different drugs. This work has been done with careful attention to ethical issues to minimize any stigmatization of the communities from which wastewater samples have been obtained by reporting loads in wastewater samples from large wastewater catchment areas[9].

Confining wastewater monitoring to large catchments may help minimize the risk of stigmatization, but it also creates issues related to data equity[8]. While data-masking procedures are meant to protect individuals in small communities or subgroups, the end result is that these smaller communities face larger data gaps or an absence of data reporting altogether. Given that wastewater data provides population-level aggregated measures, it can help close the data equity gap by simultaneously protecting privacy while making data available to smaller communities to increase sight lines into pressing public health issues. In a study of 96 wastewater treatment plants in Oregon that served 170 to 560,000 people, wastewater monitoring helped reveal that methamphetamine was not just a rural problem, and that there were no significant differences in methamphetamine use by urbanicity[10].

As NWSS continues to expand and support states in developing the infrastructure needed to monitor wastewater for public health markers, it is important to recognize that the priorities of state and local public health agencies may differ from those at the federal level. As per a survey conducted by one of the authors (in collaboration with The Rockefeller Foundation), substance use ranked third in the type of wastewater data of greatest interest to state and local public health agencies, behind new pathogenic viruses or bacteria and the influenza virus, and ahead of data on chronic diseases, antibiotic resistance, and stress, tobacco, or alcohol use[11]. Although opioid metabolites were not included in the NWSS list of prioritized targets, the programme has recognized states' desire to use NWSS funds to help address the still raging opioid epidemic, and recently began piloting wastewater monitoring for opioids in one state.

Communities could opt into the opioid expansion of the NWSS. The number of municipalities included in NWSS has greatly expanded during the pandemic, though some remain hesitant to participate in SARS-CoV-2 surveillance due to fears of stigmatization. Finding communities to participate in opioid monitoring may prove more difficult, but communities can be given the choice to opt into an opioid expansion of the NWSS. While some may opt out, due to concerns around privacy or stigmatization, others that continue to seek out better data on drug use to inform their response could benefit. Data aggregation or anonymization are other strategies that can be used to protect communities from being stigmatized. To this point, Australia's National Wastewater Drug Monitoring Program has been providing drug-use data on illicit drugs and three opioids, fentanyl, oxycodone, and heroin, for 50 anonymized locations across all Australian states and territories since 2016.

Building on existing infrastructure

From a practical standpoint, much of the wastewater monitoring infrastructure that was built or expanded during the COVID-19 pandemic to monitor SARS-CoV-2 could be readily adapted to monitor opioid use. For example, no additional funding would be needed for wastewater sample collection; the only additional cost would be to include assays for drug metabolites. For data reporting, the online Data Collation and Integration for Public Health Event Response (DCIPHER) system that states use to report wastewater data on SARS-CoV-2 concentrations could be used to report drug biomarker concentrations. The CDC has already updated DCIPHER reporting mechanisms to include data on new SARS-CoV-2 viral variants in the wastewater, and an additional or parallel platform could include drug measurements.

With respect to data interpretation, the CDC NWSS website already has much content on how to properly use and interpret wastewater data to assess SARS-CoV-2 trends. In some ways, wastewater data on opioid and illicit drug use is more straightforward to interpret than wastewater data on SARS-CoV-2 concentrations. Throughout the COVID-19 pandemic, public health officials have struggled with how to interpret wastewater data[11]. The difficulty in interpretation stems from the fact that viral RNA concentrations in wastewater cannot be readily used to estimate the number of COVID-19 cases in the catchment population, due to highly variable viral shedding rates over time and across individuals with different clinical presentation. By contrast, because the size of typical drug doses and biomarker excretion are more consistent, wastewater concentrations of opioid and illicit drug biomarkers can be converted into estimates of per-capita use, creating a more standardized and interpretable measure for public health and safety officials.

Though wastewater data on drug use can provide more intuitive metrics than wastewater data on SARS-CoV-2, it can also be more challenging to interpret because, unlike with SARS-CoV-2, communities will have underlying, endemic background signals of drug use in the wastewater as a result of prescription opioid use and therapeutic administration of opioids in hospitals. In sewer systems that accept hospital discharge, high absolute levels of opioids in wastewater may not necessarily signal illicit opioid use. For this reason, public reporting of wastewater-based opioid levels would need to account for and present data in ways that account for background therapeutic opioid use. This can be achieved by synthesizing wastewater data with data on retail sales of opioids, which are available at the three-digit zip code level on a quarterly basis. The need for such data synthesis may potentially limit opioid reporting to be quarterly, rather than near-real time, but such data would still produce more timely and granular insights into drug use trends than are currently available through other sources.

Prior to the COVID-19 pandemic, wastewater-based epidemiology was relatively rare in the United States, but coordinated, federally supported efforts led to the development of standardized protocols for SARS-CoV-2 surveillance. A similarly concerted effort to develop coordinated, standardized wastewater monitoring for opioids, methamphetamine, cocaine, and other drugs of concern would provide an objective, complementary data source on substance use in near-real time, and with minimal additional cost. Now is the time to turn our attention back to the opioid epidemic, which, unlike COVID-19, has not receded. In fact, a new fourth wave of the opioid crisis resulting from polysubstance use, including psychostimulants, was recently identified, and over a million overdose deaths are predicted by the end of this decade[12,13]. As NWSS include new sites, expanding to include new monitoring targets could put the United States at the forefront of drug surveillance, helping communities identify shifts in consumption patterns, get early warnings of new outbreaks, and have a cost-effective way to evaluate the efficacy of opioid response strategies.

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Competing interests

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