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The Potential of Wastewater Testing for Public Health and Safety

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This report summarizes research and recommendations from Mathematica's symposium on "The Potential of Wastewater Testing for Public Health and Safety," convened in Washington, DC, on May 16, 2017. The symposium included a heterogeneous panel of experts examining opioid and substance abuse through the lens of public health, public safety, and environmental issues. The meeting was designed to bridge organizational silos in order to (1) develop a common awareness of wastewater testing among entities involved in opioid policy; (2) identify knowledge gaps hampering decision making; (3) ascertain barriers to adopting wastewater testing; and (4) determine how to advance the methodology to meet current needs.

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FOREWORD

Opioid misuse has risen to epidemic levels across the United States, in part because of the ongoing difficulty of obtaining real-time information on supply and demand in the ever-changing landscape of substance abuse. Many widely used data sources, such as national population surveys, have two-year lags before the data are available. As a result, officials must operate reactively to shifts in drug diversion, abuse, addiction, and overdose. A more comprehensive strategy is needed—one that goes beyond isolationist approaches focused on individual drugs or interventions—to address the breadth and complexity of public health and safety issues surrounding substance abuse.

Municipal wastewater testing is a relatively new strategy that has the capacity to provide more rapid, comprehensive, and objective measures of drug use than are possible with current data sources. As part of a holistic approach, data from wastewater testing can shed light on multiple drugs of abuse simultaneously because a single wastewater sample can be tested for up to two dozen compounds. This methodology can be used to:

- ***Understand exposure risks*** in a community by identifying the mix of drugs being used
- ***Track population health markers*** like the flu virus, smoking, obesity, and pharmaceutical use
- ***Provide an early warning*** for emerging substances of concern by measuring changes in the mix and amounts of substances present in wastewater
- ***Assess program and policy effects*** by comparing the mix and amounts of substances used before and after the launch of an intervention
- ***Locate geographic hotspots*** by analyzing how wastewater concentrations vary across a region

Although wastewater testing cannot reveal who is using a particular drug, it can be paired synergistically with other data sources to triangulate important features of drug use. However, care must be taken when reporting the results from wastewater-based research (for example, by blinding results by site) so that communities are not unfairly identified and stigmatized.

The seminal idea of testing municipal wastewater to gauge illicit drug use came out of the U.S. Environmental Protection Agency, and in the early 2000s, the Office of National Drug Control Policy conducted one of the first proof-of-concept pilot studies. But despite its American roots, wastewater testing remains a largely untapped source of objective information on substance use in this country. In contrast, this type of testing is routinely used by the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) as part of a multi-indicator monitoring and alert system. And across Europe, Australia, and Asia, wastewater-based research is conducted under best-practice protocols developed by the Sewage Analysis CORe group Europe (SCORE).

To explore ways to capitalize on the full potential of wastewater testing, Mathematica Policy Research organized a symposium on "The Potential of Wastewater Testing for Public Health and Safety."[1] We assembled a panel of experts working on opioid and substance abuse topics in federal, state, and local government agencies, public health and safety organizations, academic institutions, and evidence-based research groups, as well as wastewater researchers from the U.S., Europe, and Australia (see Appendix A for a detailed participant list). During daylong discussions, the panel identified two broad impediments in current work to control substance abuse: (1) data inadequacies and (2) operational inefficiencies.

Wastewater-based research addresses data inadequacies in three ways, as discussed in Chapter I of this report. It can provide data in near-real time using a consistent methodology, which facilitates trend analyses. It also collects data

[1] To access the symposium materials, visit https://www.mathematica-mpr.com/events/potential-of-wastewater-testing.

in an experimental manner, as opposed to administratively, and can therefore directly address the questions at hand. And it delivers spatially granular information on the amount of a substance consumed, which can be mapped to identify hotspots of use.

Beyond the need for better data sources, the panel also spoke to the need for better integration of existing sources on substance abuse (listed in Appendix B). Chapter II illustrates how advanced analytic methods may be useful for data triangulation and prediction. However, we also highlight the complexities that arise when combining data aggregated at different geographic scales and collected with differing frequencies.

Finally, in regard to operational inefficiency, the group voiced concerns over the lack of harmonization of efforts to address opioid misuse, which drains available time and resources. Greater coordination would be helpful to target limited resources, surmount regulatory hurdles, and facilitate knowledge sharing across borders based on legal, political, and operational architectures. As discussed in Chapter III, wastewater-based research, too, requires multidisciplinary cooperation—a requirement that has historically hindered the research. But the strategy is cost-effective because it relies on existing sampling and testing infrastructure. Moreover, the consistency of infrastructure across the U.S. allows wastewater testing to be fairly efficiently scaled up for regional or national monitoring.

As a whole, the panel confirmed the potential of wastewater testing to improve substance abuse investigations. But concerns, needs, and gaps mentioned by participants during the symposium warrant additional research. Based on their collective input, we believe the following research is needed to satisfy lingering questions and encourage the adoption of wastewater testing across the United States:

1) **Develop evidence of the policy value of wastewater testing:** A proof-of-concept pilot study is needed to explicitly demonstrate the types of decisions that can be made with more rapid and geographically precise data from wastewater testing. For example, the Australian Criminal Intelligence Commission is using results from their National Wastewater Drug Monitoring Program to assess operational priorities and measure the impact of law enforcement efforts by calculating what percentage of drugs consumed in a population were seized by agents. The pilot study would also be useful to highlight operational feasibility and develop a model for working collaboratively with community stakeholders.
2) **Produce a cost-benefit analysis of wastewater testing:** Information on the policy value of wastewater testing can be readily used to determine the added value of this novel data source for state and local governments. Indeed, if wastewater testing enables more rapid responses that could reduce annual spending on opioid misuse by even 1 percent—amounting to $550 million nationally[2]—the data would pay for itself many times over.
3) **Conduct gap analyses:** Detailed comparative analyses of drug use prevalence and trends based on data from traditional sources versus wastewater testing would pave the way for data triangulation. These analyses could be used to identify gaps in traditional data that wastewater data could fill, as well as areas in which replication of data and efforts should be avoided to maximize efficiency.

Acknowledgments

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– Aparna Keshaviah, Editor

[2] One study estimated that the opioid epidemic costs the United States over $55 billion each year. For more information, see Birnbaum, H.G., A.G. White, M. Schiller, T. Waldman, J.M. Cleveland, and C.L. Roland. "Societal Costs of Prescription Opioid Abuse, Dependence, and Misuse in the United States." *Pain Medicine*, vol. 12, 2011, pp .657–667. Available at https://www.asam.org/docs/advocacy/societal-costs-of-prescription-opioid-abuse-dependence-and-misuse-in-the-united-states.pdf.

I. WASTEWATER TESTING AS A PIPELINE TO PUBLIC HEALTH DATA

Editor's note: Although major media coverage and research has focused on the opioid epidemic, equally worrisome is the fact that 644 new drugs came into use between 2008 and 2015 worldwide, according to the United Nations' 2016 World Drug Report. Today, Americans face unprecedented exposure to deadly drugs (such as fentanyl and carfentanil); viral outbreaks (such as Zika and Ebola); and antibiotic-resistant bacterial strains (such as Clostridium difficile [CDIFF] and Methicillin-resistant Staphylococcus aureus [MRSA]). These evolving public health threats, coupled with existing epidemics like obesity and diabetes, provide one of the strongest arguments for using wastewater testing, which can be used flexibly to measure and monitor a range of compounds circulating through a population.

In this brief, U.S. wastewater researchers describe the mechanics and public health applications of wastewater testing. They cover not only the measurement of illicit drugs and opioids but also broader disease biomarkers, health behaviors, and pathogens. Although there are challenges to reliably detecting opioids in wastewater, there may be ways to improve the testing methodology. For example, given that the U.S. heroin supply comes from only two countries—Mexico and Colombia—symposium participants raised the possibility of identifying heroin-specific isotopes in order to distinguish heroin from medical morphine or codeine in wastewater samples. In the meantime, wastewater testing can be used to reliably measure methamphetamine, cocaine, MDMA, and other illicit drugs for which the testing methods have already been refined.

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BACKGROUND

What if you could get an 80 percent response rate for a survey of everyone in a community? In a sense, you can—if you test the wastewater. Roughly 80 percent of Americans are connected to sewers (Evans 2015), and the wastewater that flows through those sewers represents a pooled sample of urine, feces, and gray water from that community. Akin to a urine test at a doctor's office, an analysis of wastewater provides a measure of a community's health and the substances it consumes. Wastewater-based epidemiology has the capacity to provide data on hard-to-measure health behaviors and conditions for an entire community. But despite this potential bounty of information, wastewater is an underdeveloped and underused resource in public health and safety research.

Chemical markers for health, stress, diet, chemical exposure, and drug use are examples of compounds that are excreted in urine and feces. These compounds are flushed into the sewers and travel through a network of pipes and pumps until reaching the wastewater treatment plant. It's at this point—the entrance to the plant—that sampling can occur for wastewater-based epidemiology. Sampling can also occur upstream to parse out habits for a smaller segment of the community, although this comes with added costs associated with more complicated sampling methods, more samples to analyze, complex data integration and interpretation, and potential ethical issues related to stigmatizing smaller populations (Hall et al. 2012).

A Complementary Method

Sewer systems carry wastewater from homes, businesses, and factories, typically to a centralized treatment plant. The geographic bounds of sewer catchment areas are well-documented and generally fall within established municipalities. This means that results from a wastewater-based approach can complement other epidemiological studies in which the participants' locations are known.

Wastewater-based studies have sampled populations ranging from millions (Thomaidis et al. 2016; Du et al. 2015) to a few hundred people in a single building or facility (Brewer et al. 2014; Burgard 2013). Study teams have found trends in the excretion of marker compounds for a given day, by the day of the week, seasonally, and annually (Ort et al. 2014a; Brewer et al. 2012; Lai et al. 2013a, 2014). Besides this flexibility, the major advantages of wastewater-based methods over traditional data sources are that they do not suffer from reporting biases, and they can produce near-real-time data that represent an entire community.

The remainder of this brief will describe the uses and mechanics of wastewater testing and provide examples of using wastewater to measure consumption of illicit drugs, especially opioids. It will discuss notable studies and findings, the limitations of wastewater-based methods in detecting drug use, and the next steps for refining these methods.

WASTEWATER AS A WINDOW INTO PUBLIC HEALTH

In the novel *Les Misérables*, Victor Hugo (trans. 1987) referred to the sewers of Paris as the "conscience of the city." For some time, wastewater has been seen as a potentially valuable gauge of a community's characteristics—particularly its health. Many researchers have noted that tracking certain classes of pharmaceutical compounds and personal care products may uncover details on prescription compliance as well as the prevalence of certain ailments and health behaviors (Gracia-Lor et al. 2017). For example, in several notable studies, Azuma et al. (2012), Leknes et al. (2012), and Singer et al. (2014) were able to track Tamiflu compliance during outbreaks of the flu. Their detection profiles were in line with physician-reported rates of flu and revealed that a great deal of Tamiflu prescribed was going unused. Researchers have also successfully assessed tobacco use by tracking the main urinary metabolites of nicotine, and their results closely matched sales-derived estimates (Rodríguez-Álvarez et al. 2014). Similar studies have been proposed for drugs used to treat cancer and for anxiety and depression medications (Gracia-Lor et al. 2017; Daughton 2012).

Researchers may also be able to infer big-picture trends in population health by analyzing wastewater. By tracking temporal and spatial patterns in the presence of broad-spectrum antibiotics and over-the-counter pain medications in wastewater, study teams can estimate population-wide rates of certain ailments. This can also be done by monitoring wastewater for biomarkers of stress produced by the body—such as isoprostanes, which are linked to oxidative stress and a risk of heart attack (Daughton 2012; Ryu et al. 2016). Recent studies show that it may even be possible to track broad trends in obesity rates and other health traits by using sewer sampling to check for changes in the microbiome of the human gut (Newton et al. 2015).

Another promising use of wastewater may be for pathogen surveillance. Researchers in Israel have been monitoring sewers for the prevalence of the poliovirus since 1989 (Manor et al. 1999), and other studies have found viruses and pathogenic bacteria, including salmonella (Vincent et al. 2007), coxiella (Schets et al. 2013), parechovirus

(Harvala et al. 2014), norovirus (Aw and Gin 2010), astrovirus (Aw and Gin 2010; Zhou et al. 2014), hepatitis (Prado et al. 2012), and most recently, Ebola virus (Lin and Marr 2017). Although wastewater testing for these pathogens is not currently routine, studies have shown a link between enteroviruses in sewage and those found in stool samples, suggesting the value of such tests for public health monitoring. Wastewater monitoring is also gaining attention as a possible way to track antibiotic resistance (Blanch et al. 2003). Although there are still uncertainties to be worked out—most notably around the dynamics of pathogens in sewers (Fahrenfeld and Bisceglia 2016)—there is nevertheless evidence that wastewater monitoring has the potential to predict, or track in near-real time, outbreaks and epidemics.

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THE MECHANICS OF WASTEWATER TESTING

Excretion and detection

When a drug is ingested, it is often metabolized in the body before being excreted. These metabolites move through the body in the blood before being excreted in urine (most typically) and in feces, ultimately ending up at the wastewater treatment plant. For example, the body converts cocaine to the metabolite benzoylecgonine and converts heroin (diacetylmorphine) to 6-monoacetylmorphine (6-MAM) and then to morphine.

Identifying these metabolites in wastewater ensures that the measurement is based on drug use, not simply on drugs that were disposed of down the toilet. For other drugs, such as amphetamine and methamphetamine, a metabolite may not be available because these drugs are mostly excreted in their unchanged, consumed form. But because flushing drugs down the toilet is uncommon, a unique metabolite is not essential to measure use of these drugs.

Sampling and testing

To gauge the amount of drug use in a community, representative samples must be obtained from a treatment plant. Plants often have protocols approved by their state regulating bodies for acquiring these samples. The protocols involve monitoring incoming wastewater flow and collecting samples routinely throughout the day that are then combined into a 24-hour flow-weighted composite sample. Measuring drug residues in a composite sample enables researchers to tally drug use on a daily basis. The samples can be analyzed right after collecting the composite if immediate information is needed, or this can be done later from a frozen sample. Although treatment plants conduct many analyses of composites daily to maintain their permits, plants are not mandated to have testing protocols for illicit drug metabolites, viruses, or other substances of interest from a public health perspective, and therefore standard protocols for these newly emerging substances have not been developed.

Per capita estimates through back-calculations

Using wastewater data to examine trends over time and differences between locales often leads to an interest in back-calculating the total use of a product or in

standardizing consumption estimates based on the size of the sampled population. To determine how many people have been exposed to an environmental toxin or have consumed a substance, researchers must first understand how the human body metabolizes that particular compound. The metabolic factors, which depend in part upon the person and how he or she took the drug, affect how much of the drug is excreted in urine and feces. As a result of this natural variation, excretion ratios can have uncertainties of up to 50 percent. Studies have been done to estimate average metabolic correction factors, but because they have small sample sizes that are often composed of regular users of the drug, the resulting estimates may not adequately represent all users.

Once the metabolic factor is known, the concentrations found in the wastewater can be used to back-calculate the average level of consumption in the population, often reported as a mass of the compound per 1,000 people. The size of the contributing population (which is the denominator of population-based rates of consumption) can change over time, and the size of the population excreting waste within a municipality differs every day. These fluctuations are not captured in static census estimates but can potentially be captured by wastewater (O'Brien et al. 2013). Researchers may be able to measure certain stable compounds excreted by humans to estimate the total number of people contributing to the sample at any given time. However, which compounds to use as population biomarkers—and whether they are globally good indicators—is still under debate.

ILLICIT DRUGS AND WASTEWATER

Measuring illicit drug use is difficult. The supply side, hidden by drug traffickers, is poorly known, as is the demand side, given that drug use is illegal and highly stigmatized. Data on drug use traditionally come from three sources: (1) surveys on self-reported use; (2) metrics involving the effects of use, such as fatal overdoses, drug treatment admissions, emergency department visits, and calls to telephone hotlines; and (3) police data on arrests and drug seizures (National Institute on Drug Abuse 1998).

A complementary way to measure illicit drug use is needed—one that removes reporting biases, identifies drugs specifically, can produce data in near-real time, and can also represent an entire community. This combination could be found in wastewater-based approaches to drug analysis.

Each of these metrics has strengths and weaknesses for representing population use. Surveys that capture users' reports about their drug use can end up leaving out many people because of reporting and sample bias. Moreover, because the content of illicit drugs is often unknown, users' reports may not match the actual drugs they consume (as has been seen in recent years with fentanyl-laced heroin and bogus pills). For metrics that measure the consequences of use, the data are time-lagged and often incomplete. And for patterns of drug use based on police data, the information may apply to only that specific region or city because of geographic differences in supply, demand, and enforcement. Furthermore, changes in regulations, the legal status of drugs, and prescribing practices can quickly halt the use of one drug and trigger the use of another (Alpert et al. 2017).

Given these limitations, a complementary way to measure illicit drug use is needed—one that removes reporting biases, identifies drugs specifically, can produce data in near-real time, and can also represent an entire community. This combination could be found in wastewater-based approaches to drug analysis.

Wastewater-based approaches first received worldwide media attention in 2005, when an Italian group quantified cocaine and its metabolite in wastewater from four Italian cities and the Po River (Zuccato et al. 2005). Based on wastewater testing, the researchers found that the national estimates for cocaine use in this catchment area were about 10 times lower than they should be. This gap was striking, raising questions about the accuracy of both approaches and leading to efforts to improve and standardize many aspects of wastewater-based research approaches. The next 10 years saw many more studies as well as a coordinated effort by SCORE, which collects measurements from more than 70 cities in over 28 countries in and outside of Europe (European Cooperation in Science and Technology 2016). Cocaine, amphetamine, methamphetamine, and 3,4-methylene-dioxymethamphetamine (MDMA) have all been reliably detected in wastewater samples, but heroin and cannabis have not. Table 1 summarizes notable wastewater studies conducted to date for illicit drug use, along with the challenges and needs related to detection.

The illicit drugs and/or metabolites most often studied with wastewater-based approaches are:

- 3,4-methylene-dioxymethamphetamine (MDMA, ecstasy, Molly)
- 6-monoacetylmorphine (6-MAM, heroin)
- Amphetamine
- Benzoylecgonine (cocaine)
- Methamphetamine
- THC-COOH (cannabis)

Opioids

There are three main classes of opioids of interest: heroin, pharmaceutical opioids, and fentanyl and related drugs. Heroin is a common drug linked to high rates of disease and death, and use has been growing in recent years (Gerrity et al. 2011). Pharmaceutical opioids, such as oxycodone, hydromorphone, hydrocodone, and morphine, are widely used and abused in the United States, and drug companies may be pursuing new markets overseas as opioid prescribing declines in the U.S. in an effort to reduce overdose and addiction. These opioids are legal and highly regulated, and so there are many data sources on distribution. Fentanyl is a common synthetic opioid used during surgery and prescribed for severe pain. Many nonpharmaceutical fentanyls—such as acetyl fentanyl and furanyl fentanyl—as well as illicitly manufactured fentanyl have entered the market since the mid-2000s, causing a major rise in overdose deaths (Rudd et al. 2016).

Wastewater testing has varying degrees of utility in revealing patterns of opioid use, depending on the compounds and the questions being asked.

Wastewater testing has varying degrees of utility in revealing patterns of opioid use, depending on the compounds and the questions being asked. For example, is the goal to detect the presence of a drug, the absolute level of a drug, trends over time in a place, or trends across places? Also, is drug use in an entire community of interest, or only within a certain group, or at a specific location or event?

Table 1:
Summary of Previous Studies on Illicit Drugs and Wastewater

Wastewater Studies & Findings	Challenges & Needs
COCAINE, AMPHETAMINE, METHAMPHETAMINE, MDMA	
• These drugs are reliably detected in wastewater, and use can be compared to survey data. • Distinct patterns of use are seen by urbanicity and time period (for example, on weekends and during vacations) in Australia and Europe (Thomas et al. 2012). • Oregon has greater cocaine and MDMA use in urban areas but no differences in meth use by type of area (Banta-Green et al. 2009).	• A study team in Oslo, Norway, obtained a well-balanced assessment of community cocaine use when using sewage analysis along with surveys and oral-fluid samples, but each source had shortfalls (Reid et al. 2012). • Wastewater can be used to identify total use of any drug at the population level but cannot provide dose estimates per person.
CANNABIS	
• Cannabis is inconsistently detected in wastewater. • An Australian study showed that use varied independent of location and season. • An ongoing study in Washington is assessing the impacts of legalization on consumption and market shares of recreational, medical, and illicit use (using data from wastewater testing and retail-purchased products) (Burgard et al. 2015).	• Cannabis is less easily detected than cocaine, amphetamine, methamphetamine, and MDMA because its main metabolite, THC (the active ingredient in cannabis), is fat soluble. This causes it to remain in the body longer, blurring the results of day-of-week analyses, and makes it more challenging to separate from wastewater. • Variation in route of consumption (for example, edibles versus smoking) can lead to a tenfold difference in the percentage excreted as THC-COOH, resulting in inaccuracies in back-calculated estimates of consumption. The issue is compounded as new products are introduced on the market.
HEROIN	
• Heroin is inconsistently detected in wastewater. • A European SCORE study showed more consistent use of heroin throughout the week compared with cocaine, MDMA, and amphetamine, which spiked on weekends (Thomas et al. 2012).	• Heroin is unstable in wastewater and quickly metabolizes into 6-MAM and then morphine, resulting in concentrations of heroin-specific metabolites that are too low to reliably detect in samples. Levels detected in various countries do not appear to correlate well with actual usage. • In some countries, heroin is prescribed to treat opioid use disorder, making it difficult to separate medical from illicit use. • Upstream samples may yield better results (as a result of less degradation and higher concentrations) than community-wide samples collected at a central treatment plant.
PHARMACEUTICAL OPIOIDS	
• Compared with other opioids, pharmaceutical opioids are relatively easy to detect in wastewater, given their high levels of use and chemical properties. • Wastewater testing could reveal the amount of prescribed drugs that are actually used, which could shed light on the extent of overprescribing.	• It's not possible to separate intended use from illegal use with data from wastewater testing alone, unless there are strong trends over time (for example, indicating weekend use) that do not line up with expected use patterns. • Combining wastewater testing with data on prescriptions and drug distribution might yield more informative estimates than studying wastewater alone.
NONPHARMACEUTICAL OPIOIDS, FENTANYLS	
• These compounds are difficult to detect in wastewater samples because their high potency means they are effective in small doses—and thus are excreted in low concentrations. • Some fentanyl-related products, such as carfentanil, are approved for veterinary use but have caused overdose deaths in humans (Rudd et al. 2016). Any identification of these compounds in wastewater would be useful.	• These drugs often cannot be detected by basic drug screens in medical settings, so comprehensive testing and standards for new compounds are required. • These compounds generally are not measured or reported until months or years after they are first used in a community—and often after they are declared illegal by the Drug Enforcement Administration. • Given the lack of licit use and high lethality, wastewater testing for these substances might be worthwhile.

LIMITATIONS OF TESTING WASTEWATER FOR ILLICIT DRUGS

Specificity. One of the main limitations of wastewater testing at central treatment plants is that the results do not reveal the characteristics of use or of the users. However, as more information is sought on the drug habits of certain populations, researchers have refined their scope and moved "upstream" to get data on smaller groups. Specific upstream studies include research at a fitness center (Schröder et al. 2010), prison (Postigo et al. 2011), hospital (Ort et al. 2010), and college (Burgard et al. 2013; Panawennage et al. 2011). In another study, researchers compared drug concentrations in wastewater from a multiday music festival versus wastewater from a nearby urban center in Australia; they found that MDMA use during the festival was significantly higher than typical urban use for two years in a row (Lai et al. 2013b). And in a study at a U.S. college, researchers looked for potential illicit use of two "smart drugs" typically prescribed for attention deficit hyperactivity disorder but sometimes used to enhance academic performance. Researchers found that concentrations of these drugs (such as Adderall) were higher during midterm and final exams.

Detection. Two problems with analyzing drug-marker compounds in wastewater are (1) their low concentration and (2) the difficulty of extracting them from the complex wastewater soup. Both problems can be solved via chemical filters used by environmental and analytical chemists (though, because these filters are not one-size-fits-all, compromises are often made to detect a large number of drug markers). Drug-marker compounds in wastewater are typically present in nanograms per liter (parts per trillion), but these filters increase the concentration of the drug compounds by 10 to 1,000 times, so their final concentrations (now in parts per billion) can be detected via mass spectrometry. Mass spectrometers have only recently become commercially available, costing between $300,000 and $500,000 and requiring skilled technicians, but they are making their way into routine use in drug-testing labs. At present, the cost of analyzing a sample obtained from a central treatment plant using mass spectrometry is at least $100. If "upstream" sampling were required (to obtain information on a more localized population), it would cost an additional $10,000 to $50,000, depending on the number of sampling locations of interest.

Stability. Researchers have run into problems testing the stability of drug markers. Many have tried to do so using wastewater samples in the lab and have tracked the degradation of drug markers over 24-hour periods at different temperatures. But wastewater in a beaker is different from wastewater in a sewer. For example, sewer walls are lined with microbial biofilms, forming and changing in both aerobic and anaerobic conditions, which are difficult to mimic in the lab. More recently, researchers have begun to closely study and model degradation of certain drug markers in transit from the point of entry into the sewer system to the point of exit at the central treatment plant, with the goal of establishing bounds around the uncertainty of drug concentration estimates due to instability of drug markers in wastewater (McCall et al. 2016; Ramin et al. 2016; Thai et al. 2014).

Degradation bias is less of an issue when tracking trends in drug use over time within a single sewer, given that the loss of compounds should stay relatively consistent from week to week or from year to year. But to be able to directly and fairly compare estimates of use between two sewer systems that have different designs or different environmental conditions, additional calibration studies would be needed.

CURRENT AND FUTURE DIRECTIONS

Given the complexities just described, it's clear that there are many sources of variability in wastewater samples: across-day sampling, within-day sampling, flow error, analytical error, degradation, population estimates, and so on. And for many compounds, the data may be censored—that is, not quantifiable or below the level of detection over many days. Researchers must include these sources of variability and any censored data in their analyses so they can provide a correct point estimate, or mean. Moreover, confidence bounds around estimates must be presented so that it's possible to compare the levels of a drug across time or place.[1]

Although wastewater testing has been well-studied for cocaine, methamphetamine, amphetamine, and MDMA (and to a lesser extent, cannabis), there is less evidence of its usefulness for opioids. This is because chemists and engineers have historically focused on compounds that seem more straightforward to analyze. But wastewater testing for illicit synthetic opioids might be more feasible if a different type of sampling was done. For example, passive samplers such as the Polar Organic Chemical Integrative Sampler (POCIS) are devices that collect small molecules, such as those of illicit drugs or their metabolites, as water moves through them. This enables the samplers to integrate concentrations over time. The device is then removed, and the metabolites are extracted.

The POCIS technique could increase the low signals in wastewater for highly potent but less common opioid drugs. However, for the sampler to integrate the concentrations over time, the markers must remain stable in the changing environment of wastewater—which is why passive samplers are unlikely to be useful for tracking heroin or its metabolite. Researchers would need to determine the stability of many of the new synthetic opioids to assess whether these samplers can detect them. The resulting data would be binary (indicating the presence or absence of a drug) and thus may be useful only for a limited set of research questions.

High-resolution mass spectrometry (HR-MS) is being used more often to quantify illicit drugs or other compounds of environmental concern. HR-MS measures the exact mass of compounds, which adds specificity to the analysis and thus helps researchers determine targeted compounds with a higher degree of confidence. In addition, HR-MS can identify substances in the wastewater without necessarily needing a chemical standard for comparison (Bade et al. 2016). As a result, a new drug or contaminant that surfaces in the community could be found with HR-MS before it's known to users or authorities.

As these sensors become cheaper and more robust, they could support the routine monitoring of pathogens, illicit drugs, and other biomarkers of public health. Their high specificity may help detect low concentrations of targeted, known opioids.

For opioids, a more recent and promising advance in wastewater monitoring is the development of DNA-based sensing devices. These devices rely on biological receptors (such as DNA, antibodies, or proteins) that produce a signal when they bind in a certain way with an analyte of interest. They have the potential to work somewhat like a simple pregnancy test and thus may facilitate on-site, near-real-time monitoring by unskilled personnel (Yang et al. 2015). The use of these sensors in the medical field is becoming routine, and one such sensor has recently been developed to track cocaine in wastewater (Yang et al. 2016).

Such approaches are still in their infancy, though; they are fairly expensive and can be easily rendered ineffective by the vast number of other compounds in wastewater. But as these devices become cheaper and more robust, they could support the routine monitoring of pathogens, illicit drugs, and other biomarkers of public health. Their high specificity may help detect low concentrations of targeted, known opioids. A trade-off, however, is that the specificity of the approach makes these devices ineffective for identifying new, unknown synthetic compounds.

CONCLUSIONS

Offering near-real-time analysis and representative sampling of a population, wastewater-based methods add value to the current tools used to estimate illicit drug use. These methods can be used to monitor trends in drug use at a population level and, for a growing number of drugs, produce consumption estimates that line up with estimates derived from other metrics—but with faster results.

With respect to opioids, major challenges remain in answering basic and important questions, such as determining whether heroin was involved in an opioid death (Harruff et al. 2015). To refine wastewater testing for opioids, more research is needed on ways to optimize sample collection and lab analytic methods to better detect these drugs. And as new opioid formulations emerge, pharmacokinetic studies will be needed to better estimate excretion factors and degradation rates in sewers. Wastewater could help answer these questions, but it will be important to focus on the highest-priority questions and information gaps to determine whether and when wastewater testing adds value to opioid epidemiology and drug policy.

II. PREDICTIVE POWER: USING ADVANCED ANALYTICS TO ENHANCE DECISION MAKING

Editor's note: Increasingly, we have at our fingertips an abundance of tools for predictive modeling. For example, machine-learning algorithms have proven valuable in a variety of fields, from entertainment to ecology to economics. But to perform well, these algorithms must be trained on large, detailed, and objective datasets—for even the best algorithms will go awry when applied to data that reflect our blind spots and biases. In the following brief, a team of Mathematica analysts summarize the results and challenges of a predictive modeling exercise based on data in the public domain. We attempted to use machine learning and data triangulation to predict opioid overdose deaths across Massachusetts. Although our models did a fair job of predicting the ranking of a city or town based on its rate of opioid deaths, they fell short in predicting the actual magnitude of deaths. Our predictive power was curtailed by a lack of nuanced information in existing datasets.

Because wastewater can provide more objective measures of drug use than population surveys plagued by self-reporting and recall biases, it is particularly well-suited for machine-learning approaches. Furthermore, the capacity of wastewater testing to measure multiple substances at once can be harnessed through analytics to identify new drug combinations and drug substitutions, thereby helping us better understand population risks. When integrating wastewater data with existing data sources, though, adjustments must be made for geographic differences between a wastewater treatment plant's catchment region and the county boundary within which it resides.

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BACKGROUND

Public health and criminal justice officials at all levels of government are working to curb opioid misuse. But despite their efforts, overdose deaths continued to rise between 2014 and 2015, and overdoses remain the leading cause of accidental deaths (Rudd et al. 2016a). Multiple actors will need to coordinate their efforts to temper this trend. To reduce the risk of addiction, health care providers will need to curtail unnecessary opioid prescriptions, take note of patients' histories of substance abuse, and facilitate treatment receipt for patients who are addicted to opioids. Criminal justice officials will need to curb the supply and sale of heroin and fentanyl and support the transition to treatment for people with opioid addiction who enter into the criminal justice system. Finally, treatment providers for substance use disorder will need to expand their capacity, increase the use of evidence-based treatment, extend the continuum of care to address the chronic nature of opioid disorders, and increase outreach to more people in need. Collaboration between these actors—supported by integrated data systems—will improve resource targeting and program efficacy.

Recognizing the need for a multifaceted, collaborative approach to address the opioid epidemic, we sought to use advanced analytics to support decision makers by creating a tool to predict fatal opioid overdoses. The tool synthesizes public health and law

Analyses at the community level may help support policy decisions that are often made at the community level, such as where to establish a new treatment facility, allocate staff, or launch a prescription take-back program.

enforcement data in order to give decision makers the information needed to target resources to communities at the greatest risk for opioid deaths. We hypothesized that combining multiple datasets from federal and state agencies would paint a more complete picture of the factors contributing to the epidemic than could any given dataset used alone.

We focused our analysis at the community level in order to assess the value of publicly available data sources, which are typically aggregated at the city, county, or state level. This type of analysis may help support policy decisions that are often made at the community level, such as where to establish a new treatment facility, allocate staff, or launch a prescription take-back program. Moreover, community-level data can be more accessible than other types of data for research and policymaking.

The remainder of this chapter provides more detail on our methods, the accuracy of our predictions, the challenges encountered, and potential extensions of our approach.

METHODS

The main goal of our analysis was to give decision makers information that would enable them to target resources to the communities with the greatest needs. We used the community-specific rate of opioid deaths as a proxy for need, thus creating a model to predict the opioid death rate. We focused on Massachusetts because it has one of the fastest-growing rates of fatal opioid overdoses in the country, ranking eighth in the United States for opioid deaths (Rudd et al. 2016b), and it also provides high quality, publicly available data from diverse sources reported down to the level of the city or town.

During our analysis, we encountered four key challenges related to the following:

- ***Multidimensionality*** *(Identifying and integrating data from multiple sources)*. We identified a number of datasets reporting measures at the city or town level, which was our level of analysis. For county-level covariates from the Massachusetts Prescription Monitoring Program (MA PMP), we adjusted values based on the fraction of the county's population represented by each city or town.

- ***Geography*** *(Accounting for spatial dependency in the outcome)*. Residents and resources (such as transportation and medical care) cross city and town boundaries; as a result, neighboring cities and towns are expected to have more similar opioid death rates than more distant cities and towns, even after controlling for demographics and other covariates. We incorporated this spatial dependency into our models to increase the accuracy and precision of our estimates.

- ***Modeling framework*** *(Selecting an appropriate statistical model for predictions)*. A range of frameworks exist for predictive modeling, each with advantages and disadvantages. We selected frameworks for modeling that lined up with our modeling goals and chose a final framework that maximized our predictive power.

- ***Forecasting*** *(Accurately assessing the model's predictive power).* We created a robust framework a priori for model specification and refinements.

Multidimensionality

To account for the diverse factors that could cause a fatal opioid overdose, we identified a variety of datasets and candidate predictors. Given that nearly half of all opioid overdose deaths involve a prescription opioid (Centers for Disease Control and Prevention n.d.), we hypothesized that the frequency of opioid prescriptions would be an important predictor of these deaths. We also included information on treatment for opioid addiction as a predictor. Finally, as a proxy for opioid misuse or the diversion of opioid prescriptions, we considered drug-related crimes in our model. Links between these factors and opioid overdose deaths have been observed in analyses conducted at the individual and state level (Massachusetts Department of Public Health [MA DPH] 2016a; Paulozzi et al. 2011). Moreover, in trend analyses, large increases in opioid diversion and abuse from 2002 to 2010—which then flattened or fell from 2011 through 2013—mirrored rises and falls in opioid-related deaths (Dart et al. 2015). We also examined the influence of demographic factors on opioid deaths, given observed differences in opioid prescribing and opioid-related mortality by race (Case and Deaton 2015) and by disability status (Jones et al. 2016), for example.

Our analysis drew on rich datasets from agencies across Massachusetts as well as state-specific data reported in national datasets (Table 1). All variables were aggregated to the city or town level. For our outcome—the opioid death rate in a city or town—data on the number of opioid deaths in each city or town (MA DPH 2016b) were augmented with data on the annual population for each city or town (MA State Data Center n.d.) to enable us to calculate deaths per 100,000 people. For model covariates, we extracted data on opioid prescriptions from the MA PMP (MA DPH n.d.), on admissions for opioid addiction treatment (Massachusetts Bureau of Substance Abuse Services [MA BSAS] n.d.), on drug/narcotic offenses related to crimes against society (National Incident-Based Reporting System [NIBRS] 2014), and on demographics, based on the 2011-2015 American Community Survey (ACS) 5-year estimates (United States Census Bureau n.d.).

The ACS contained complete demographic data for all cities and towns in Massachusetts except North Attleboro, which was consequently excluded from our analyses. BSAS variables on addiction treatment were missing for 17 and 19 percent of Massachusetts communities in 2013 and 2014, respectively. We believe that missing values were a result of suppressing data based on small sample sizes (to protect client confidentiality) and/or because BSAS only collects data from its contracted providers, which means that outpatient treatment data does not include non-BSAS-paid services (MA DPH 2016c). NIBRS variables on drug-related crimes were missing for 24 and 29 percent of the communities in 2013 and 2014, respectively. For this dataset, missing values were likely due to the fact that data reporting by police agencies was voluntary, and only about half of the full-time agencies in Massachusetts routinely submit their crime data to NIBRS. For both the BSAS and NIBRS datasets, the mechanism of missing data supported our assumption of missingness at random, which enabled us to use

multivariate imputation by chained equations to impute missing values for both years (van Buuren 2007). Imputation allowed us to retain these cities and towns in our analyses.

Table 1:
Data sources and variables used to predict opioid-related death rates

Domain	Source	Variables
Fatalities	MA DPH	• Number of opioid overdose deaths (per 100,000 residents)
Prescriptions	MA PMP	• Number of Schedule II opioid prescriptions (per 100,000 residents) • Number of Schedule II opioid solid dosing units (per 100,000 residents) • Percentage of people with a Schedule II opioid prescription • Percentage of people with a Schedule II opioid prescription who have "activity of concern"[a]
Addiction	MA BSAS	• Percentage of drug treatment admissions with opioids as the primary drug
Diversion	NIBRS	• Number of total offenses (per 100,000 residents) • Number of crimes against society (per 100,000 residents) • Number of drug or narcotic crimes against society (per 100,000 residents)
Demographics	MA State Data Center	• Population per city/town in Massachusetts
	ACS 5-year estimates	• Median age • Median income • Percent male • Percent by racial/ethnic category (White, Black, Asian, American Indian/ Alaskan Native, and Hispanic) • Percent below the poverty level • Percent uninsured (among the non-institutionalized population) • Percent unemployed (in the civilian labor force) • Percent disabled among the non-institutionalized population • Percent with an ambulatory disability • Percent with public health insurance only[b] • Percent with Medicare coverage only

[a] "Activity of concern" is defined as the receipt of at least one Schedule II opioid prescription from four or more different prescribers that are filled at four or more pharmacies.

[b] This group includes people covered only by the federal programs Medicare, Medicaid/means-tested coverage, or VA Health Care (provided through the Department of Veterans Affairs).

Geography

To account for the spatial dependency in the rate of opioid overdose deaths across the cities and towns, we examined three metrics: (1) the latitude and longitude corresponding to the geographic center of each city or town; (2) the distance from Boston, the capital and largest city in Massachusetts, which likely has unique resources that are more accessible to nearby cities and towns; and (3) the average rate of opioid deaths across adjacent cities and towns, based on prior-year data. We calculated each metric using geographic information system (GIS) data (which provides information on the boundaries of each city or town), and we identified adjacent cities and towns based on any shared boundary, according to MassGIS (MA Office of Geographic Information 2004).

When evaluating different modeling frameworks, a useful aspect to consider is the trade-off between interpretability and predictive accuracy.

Modeling framework

We explored the predictive power of several types of statistical models, ranging from a more traditional Poisson regression model to advanced machine-learning approaches like decision tree models (Figure 1). When evaluating different modeling frameworks, a useful aspect to consider is the trade-off between interpretability and predictive

accuracy. For example, estimates from a Poisson regression model can be interpreted fairly intuitively, but this model often leads to poorer predictions compared with other machine-learning approaches because of the need for strict parametric assumptions that may not be reasonable.

Figure 1:
Prediction models evaluated

More interpretable

Better predictions

Model type	Description
Poisson regression	A generalized linear model form of regression analysis used to model count data.
Least absolute shrinkage and selection operator	A method of regression analysis that performs regularization (to reduce model overfitting) through variable selection
Ridge regression	A method of regression analysis that performs regularization by minimizing the influence of unimportant predictors
Generalized additive model	A generalized linear model in which the predictor depends on unknown smooth functions of covariates
Recursive partitioning	A statistical method for creating a decision tree that classifies observations
Random forest	An ensemble learning method that constructs a collection of decision trees

Note: This information is based on the authors' collective experience and insights from literature such as Caruana et al (2015).

Forecasting

We developed a predictive model using data from 2012 to 2014, and based on this model, we sought to predict opioid-related death rates in 2015—the most recently available data at the city or town level at the time of the analysis. To ensure that our modeling was not overly specific to the historical data available, we used the following three-stage process for modeling based on partitioned data (Figure 2):

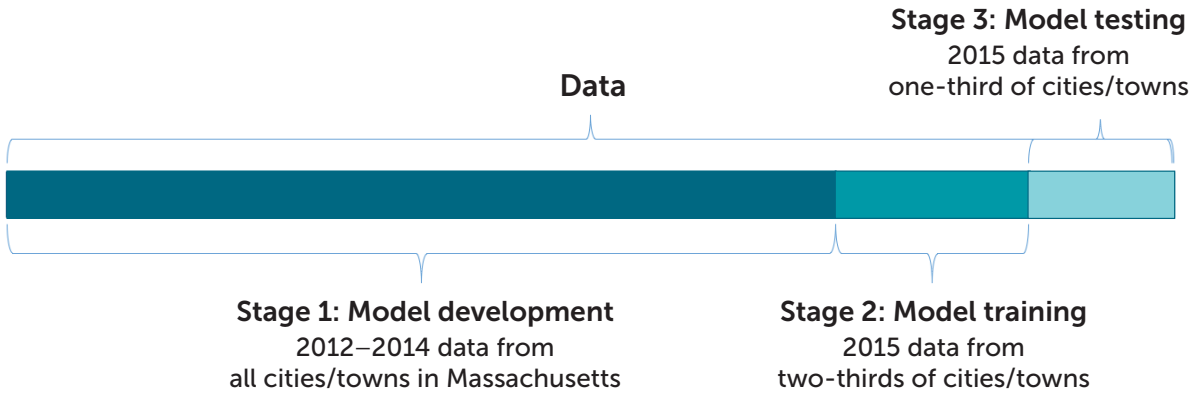
Stage 1: Model development. In this exploratory stage, we used covariate values from 2012 and 2013 to predict 2014 rates of opioid deaths. In developing our model, we (1) explored the association between candidate predictors and our outcome to determine which covariates to include, (2) determined the best functional form for covariates (for example, deciding whether to include median age or variables for age categories), and (3) examined whether including multiple years of covariate data improved predictions.

Stage 2: Model training. Next, we fit our preliminary models to a "training" dataset composed of 2015 opioid fatality rates for two-thirds of Massachusetts cities and towns (n = 233). All models included the previous year's rate of opioid deaths. Then, in a fashion similar to the Stage 1 modeling, we examined how prior-year covariate values improved our predictions of 2015 rates of opioid deaths. To evaluate the performance of different modeling frameworks and choose a final model, we used the root-mean-squared error (RMSE) of prediction. RMSE is calculated as the average squared difference between predicted and observed rates of opioid deaths across cities

and towns, with a lower value indicating better model performance. We also generated model diagnostics (such as plots of observed versus predicted values by community size) to determine if our models required refinement (returning to Stage 1) or were ready for validation (proceeding to Stage 3).

Stage 3: Model testing: We validated our final model using a "testing" dataset composed of 2015 rates of opioid deaths for the remaining one-third of cities and towns (n = 113[3]). We compared how the RMSE of our final model changed when based on the testing versus training dataset; examined maps of predicted versus observed values across Massachusetts; and assessed how well our final model performed by community size, examining the accuracy of our predictions for both small towns and large cities.

Figure 2:
Predictive analytic framework



Results

During model development (stage 1), we decided to include the median age and median income in our models rather than age or income groups because the former had comparable predictive power to the latter and simplified the model. We also found that including covariate values based on 2012 data did not improve predictions over including 2013 data alone, and thus we chose to use only prior-year covariate data in our final model.

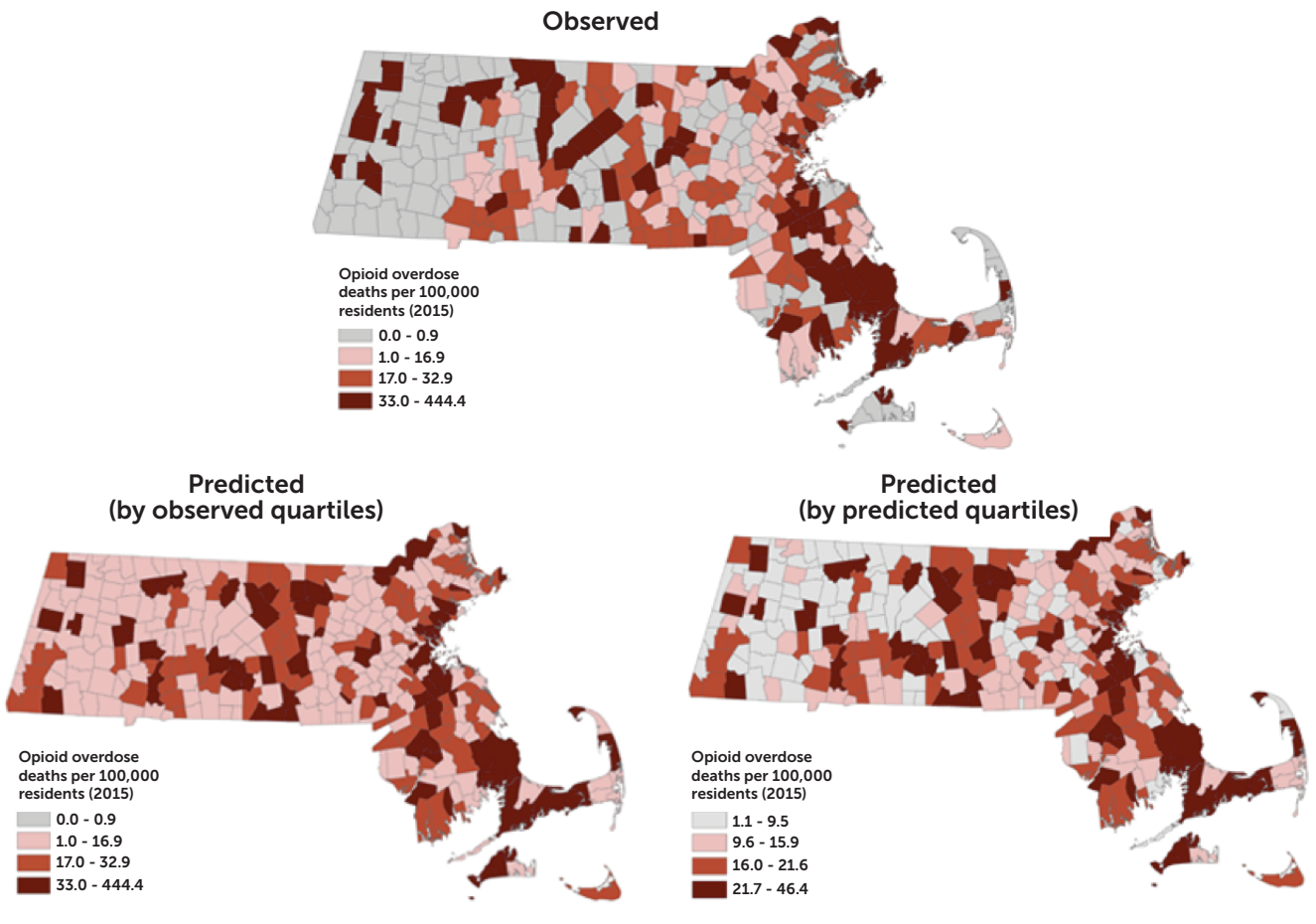
During model training (stage 2), we compared the performance of different frameworks for models that included various combinations of the covariates listed in Table 1 plus the metrics to capture spatial dependency. We found that the worst performing model was a Poisson model that included the prior-year rate of opioid deaths plus demographic characteristics and all three spatial metrics (RMSE 22.5). By contrast, the best performing model—our final model—was a random forest model that included the prior-year rate of opioid deaths, all covariates listed in Table 1, and

[3] The testing dataset was actually composed of 117 cities and towns, but we excluded 4 because they had over 80 opioid deaths per 100,000 per year and were considered extreme outliers.

the spatial metric capturing the average opioid overdose death rate across adjacent cities and towns (RMSE 15.4).

In the final modeling testing stage (stage 3), we re-ran the random forest model using data from the testing dataset. The RMSE changed very little (RMSE 15.7), indicating that our data-partitioning strategy worked well to ensure that our final model was not overly specific to the available data. We next compared the observed 2015 rates of opioid deaths for each city and town in Massachusetts (Figure 3, top panel) with the predicted rates based on our final random forest model (Figure 3, bottom panels). The predicted rates can be presented a number of ways. In the bottom-left panel, we color-coded communities based on quartiles of the *observed* 2015 rate of opioid deaths, whereas in the bottom-right panel, we color-coded communities based on quartiles of the *predicted* 2015 rate.

Figure 3:
Observed and predicted rates of opioid overdose deaths across Massachusetts



The noticeable difference between observed and predicted rates when using the same quartile scheme for color-coding suggests that our model did not do a very good job of predicting the actual magnitude of opioid-related deaths. However, the similarity between the observed and predicted maps when using the data-specific quartile scheme for color-coding suggests that our model did better at ordering the towns from lowest to highest predicted rate of opioid deaths. Further inspection of the results indicates that the predictive model is overestimating communities with low opioid-related fatality rates while underestimating communities with high rates—a common phenomenon in statistical modeling called *regression to the mean*.

Finally, to determine which variables and datasets added the most predictive value in our analysis, we examined changes in the RMSE based on including or excluding our hypothesized predictors. To our surprise, variables with information on prescriptions, addiction, and drug diversion were only slightly correlated with opioid death rates; these variables added little predictive power to the model, leaving the RMSE virtually unchanged when they were removed.

DISCUSSION

Our goal was to assess whether we could develop a tool that would help decision makers target opioid prevention and treatment resources to the communities with the greatest need. Our final model did a fair job predicting the ranking of cities or towns by their rate of opioid deaths—but not in predicting the magnitude of these deaths. The findings suggest that, although our models maximized the predictive potential of the available data, refinements in the model inputs and framework are needed to improve predictive accuracy. Somewhat surprisingly, we did not see a strong relationship between any of our hypothesized predictors and our outcome. This could be because we relied on data sources easily accessible in the public domain, and these sources did not contain sufficient detail for our predictive analyses, as described below.

Data that are available publicly typically contain aggregate metrics to sidestep privacy concerns associated with individual-level data. But aggregation can end up combining effects that trend in opposite directions, thus "washing out" the overall effect.

Data limitations

Data that are available publicly typically contain aggregate metrics to sidestep privacy concerns associated with individual-level data. But aggregation can end up combining effects that trend in opposite directions, thus "washing out" the overall effect. For example, research indicates that deaths associated with heroin use increased from 2010 to 2013, while deaths associated with prescription opioids decreased in the same timeframe (Dart et al. 2015). But our analyses based on available MA DPH data were confined to an aggregate measure of opioid-related deaths that included those associated with both prescription opioids and heroin.

The aggregate-level data we analyzed also lacked sufficient detail to capture important relationships between variables. For example, MA DPH (2016) found that the risk of a fatal opioid overdose was 56 times greater among previously incarcerated people than among the general public, with the greatest risk in the first month after release. The NIBRS dataset we analyzed included information on the proportion of people in each city or town with a drug or narcotic offense, but we could not directly link overdose death status and previous incarceration status at the individual level.

Additionally, our aggregate-level data may not have been detailed enough to capture the sequence of effects between variables. For example, increases in drug or narcotic offenses over time may be due to increases in illegal drug activity which, in turn, is correlated with increased overdose deaths. Or it may be due to increased enforcement activity, which might be reducing overdose deaths because of early intervention. Our model would have benefitted from having a refined measure of illicit opioid use in which the direction of change in the measure is expected to induce a clear, unidirectional change in opioid deaths. Similarly, our data were not sufficiently detailed to include information on overdose and treatment history, such as the fact that, according to MA DPH (2016), people who received opioid agonist treatments after a nonfatal overdose were significantly less likely to die from an opioid overdose than those not receiving such treatments.

Finally, the accuracy of our predictive models could also have been improved by having more timely data. Data reported on a monthly or quarterly basis may better capture the relationships between changing factors than data collected annually (as used in our analysis). This is particularly true in years when community-level interventions are introduced. For example, if the launch of a take-back program for unused prescriptions weakens a direct relationship between opioid prescriptions and opioid deaths, that differential effect (before versus after the intervention's launch) may not be captured in an annual dataset that aggregates data across both time periods. With additional time and resources, it would have been useful to identify data that were measured more frequently. However, when merging data with different reporting frequencies, researchers must take care to maintain data granularity, and should consider whether imputation is needed.

In a future extension of our modeling approach, researchers could consider proxy outcomes that may be more reliably reported than opioid deaths, given that death certificates greatly understate the involvement of opioids in overdoses.

Extensions to modeling opioid overdose deaths

Just as the use of multiple datasets and data triangulation may help close the gaps in any single dataset, so too could the use of multiple outcome measures help overcome the shortcomings of any one measure of opioid misuse. For example, death certificates are an unreliable source of information on the opioid overdose death rate because they greatly understate the involvement of opioids in fatal overdoses (Ruhm 2016). And self-reported survey data on drug use is prone to under-reporting and misattribution—not only because of stigma but because people may not always know what drugs they have taken (as is often the case with fentanyl-laced heroin).

A proxy measure linked to opioid abuse may help researchers sidestep such issues. For example, spikes in new cases of HIV were seen in the rural Indiana town of Austin in 2015 due to the use of contaminated syringes when injecting heroin or other opioids. In fact, a report by Harm Reduction International estimated that HIV prevalence is 28 times higher in people who inject drugs compared with the rest of the population (Henry 2016), and based on statistics from the United Nations Office on Drugs and Crime in their World Drug Report (2016), one in 10 new HIV infections worldwide

occur in people who inject drugs. Accordingly, HIV or hepatitis C (which has also increased in recent years alongside opioid misuse) could be useful as proxy measures for opioid misuse. These infectious diseases in particular may be reliable and more consistently reported than drug overdose data because they are required by state law to be reported to the Massachusetts Department of Public Health.[4] A future extension of our modeling approach could consider predicting rates of these proxy outcomes to identify communities with the greatest need.

CONCLUSIONS

Advanced analytic techniques can be used to combine information from many different sources. However, as illustrated by our analysis, the power of a predictive model is only as good as the data that feed into it. Predictive modeling would benefit from having more granular and timely data in the public domain and from incorporating multiple outcome measures to increase model robustness.

[4] For a complete list of infectious diseases reportable in Massachusetts, see http://www.mass.gov/eohhs/docs/dph/cdc/reporting/rprtbldiseases-hcp.pdf.

III. SUCCESSES AND HURDLES IN INTERNATIONAL WASTEWATER STUDIES

Editor's note: Data from wastewater testing can be used to address shared goals between public health and public safety officials. For example, wastewater data enables near-real-time surveillance that can be used to identify emerging substances that put communities at risk. Moreover, its capacity to yield actionable intelligence for public safety does not compromise the ability of public health researchers to study broad patterns and long-term trends in substance abuse. However, cooperative data use agreements and sampling and testing plans will need to be established at the outset to ensure that both near-term and long-term goals are served by the data obtained.

In this final brief, representatives from the European-wide SCORE and EMCDDA groups summarize the infrastructural, logistical, and collaborative requirements of wastewater-based epidemiology; strategies for meeting these needs; and opioid-specific findings from international wastewater studies on drug use. Beyond the expertise of wastewater researchers, this work also requires the input of the operators at wastewater treatment plants; staff at testing labs; local government officials; funding agencies; and experts in the fields of epidemiology, statistics, public health and medicine, public safety and law enforcement, and communications.

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BACKGROUND

Wastewater-based epidemiology (WBE) is a novel approach to capturing public health data by analyzing urban wastewater for certain metabolic products, or biomarkers, excreted by humans (Castiglioni et al. 2014). As a sort of "collective" urine test, wastewater testing involves examining a pool of anonymous urine samples, often from hundreds or thousands of people. The most popular use of WBE is to estimate illicit drug use in a community, as first attempted by Zuccato et al. (2008) and later implemented worldwide with promising results (Banta-Green et al. 2009; Thomas et al. 2012; Ort et al. 2014a; Lai et al. 2016).

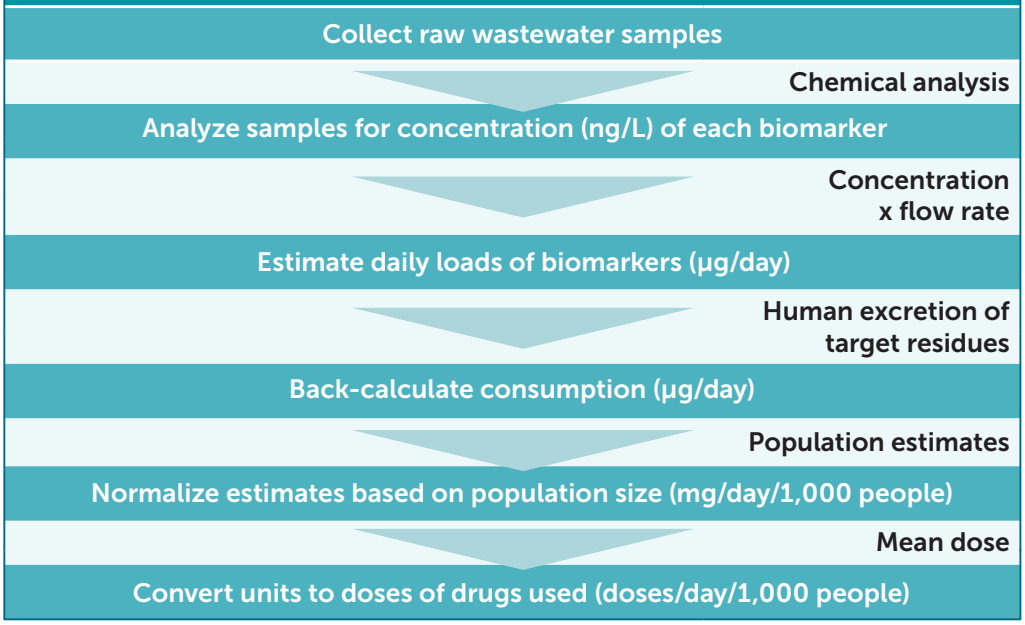
WBE involves identifying and quantifying specific biomarkers and back-calculating the amount of the corresponding illicit drugs that have been consumed by a population served by a wastewater treatment plant (WWTP) (Figure 1). Researchers have successfully used WBE to track temporal and spatial trends in drug use at different geographic scales, to provide updated estimates of drug use, to identify changes in drug habits, and to quantify the use of new substances (Castiglioni et al. 2014). The method is particularly useful for monitoring a hidden and stigmatized behavior like drug use because it enables researchers to sidestep the barriers posed by self-reported data, such as inaccuracies and reporting delays. It is therefore a valuable tool in the epidemiological toolkit for tracking drug habits and identifying the emergence of new psychoactive substances (EMCDDA 2016).

In Europe, EMCDDA includes WBE among its drug use indicators and supports a yearly monitoring program, the results of which are published in annual reports

Wastewater-based epidemiology has also been adopted in Australia as part of a National Wastewater Drug Monitoring Program, which is used by the Australian Criminal Intelligence Commission and the Australian government to monitor the use of several substances across the country.

and on the EMCDDA website.[5] WBE has also been adopted in Australia as part of a National Wastewater Drug Monitoring Program, which is used by the Australian Criminal Intelligence Commission and the Australian government to monitor the use of several substances across the country.[6]

Figure 1:
Steps involved in wastewater-based epidemiology



A BEST-PRACTICES PROTOCOL FOR WBE

In 2010, a group of European researchers established the SCORE network to coordinate international studies, the first of which was conducted in 2011 (Thomas et al. 2012). At the time, this multicity study posed several major challenges related to different sewer networks servicing each city's WWTP, different sampling procedures, different methods for quantifying drug levels, and the varying quality of the data sources used to define the population of the WWTP catchment areas. SCORE was able to mitigate many of these challenges by developing a best-practices protocol, using a questionnaire to characterize each sewer catchment area, and establishing an interlaboratory comparison scheme.[7]

SCORE created its protocol after evaluating the uncertainties associated with each step of the WBE approach. These included uncertainties related to sampling, biomarker analysis and stability in wastewater, back-calculation of per capita drug

[5] See http://www.emcdda.europa.eu/activities/wastewater-analysis.

[6] For details on the program, visit https://www.acic.gov.au/publications/intelligence-products/national-wastewater-drug-monitoring-program-report.

[7] To access the consensus protocol for sampling, analysis, and reporting, see the Guidelines section here: http://www.emcdda.europa.eu/activities/wastewater-analysis#pane4.

use, and estimation of population size (Castiglioni et al. 2013). The protocol was designed to control and minimize these uncertainties and harmonize all procedures, and was revised after several successive analytical campaigns in Europe. SCORE's main improvements were to:

- ***Standardize the sampling methods*** by evaluating the effect of different sewer designs and sampling procedures on the data gathered, and establishing a sampling protocol (Ort et al. 2014b)
- ***Control the quality of analytical results*** by conducting yearly interlaboratory studies among labs running chemical analyses of wastewater samples; results from a lab are accepted only if specific quality control criteria are met[8]
- ***Establish WBE biomarker requirements***, including evaluating drug stability in wastewater and pharmacokinetic profiles to develop suitable correction factors (Gracia-Lor et al. 2016, 2017)
- ***Address ethical issues*** related to WBE studies (Prichard et al. 2014) and establish ethical research guidelines[9]

Most of these activities are done by the SCORE Cooperation in Science and Technology (COST) network (specifically, COST Action ES1307[10]) through annual monitoring campaigns, working group activities, training schools, short scientific missions, and periodic meetings that are open to participants worldwide. To date, two international multidisciplinary conferences have been organized on WBE methods. These events provide a unique and valuable opportunity for experts from different areas to discuss critical issues, the use of wastewater analysis for drug epidemiology, and extensions of this method to new applications. The third international conference will be held in Lisbon, Portugal, in October 2017.[11]

LOGISTICAL CHALLENGES OF INTERNATIONAL STUDIES

Since 2011, SCORE has conducted annual week-long monitoring studies, with the number of participating cities growing from 19 in 2011 to more than 70 in 2016. Under the current design of the SCORE monitoring program, labs that meet the study requirements for interlaboratory quality control can analyze wastewater samples from a number of cities and submit data to SCORE for collation.

This approach works well when participating cities and countries have labs with established analytical capacity. But when new cities or countries are added to increase geographical resolution, their wastewater samples must either be sent to established labs for analysis (which is the more straightforward way to incorporate samples from new areas), or new labs within that city or country must be certified and incorporated

[8] See http://score-cost.eu/monitoring/interlab/ for results from interlaboratory testing.

[9] The ethical guidelines are available at http://score-cost.eu/ethical-guidelines-for-wbe/.

[10] For details, see http://score-cost.eu/about-us/es1307-action/.

[11] Information about the third conference are available at http://score-cost.eu/network-activities/meetings/ttw2017/.

into the network (which increases analytic capacity overall). A third option is to organize staff exchange programs in which researchers visit collaborating labs for a few weeks. Doing so enables new labs to implement robust and accurate analytical methods faster than trying to do this on their own. The quality of the data generated by any new labs is assessed using the interlaboratory scheme described previously. If new labs fail on their first attempt, their data are excluded from SCORE analyses and reports.

A strong working relationship with wastewater treatment plant staff is necessary to be able to collect high quality samples and data on the sample collection environment (such as flow data and catchment maps for obtaining population estimates).

Being able to easily collect and analyze wastewater samples is key to making wastewater testing a routine process. In our experience, this requires a good relationship with a WWTP. Local jurisdictions or private companies often run WWTPs, and as such, certain approvals or confidentiality agreements may need to be in place before sampling can occur; a good rapport can help this process go smoothly. A strong working relationship with WWTP staff is also necessary to be able to collect high quality samples and data on the sample collection environment (such as flow data and catchment maps for obtaining population estimates). For example, lab personnel sometimes set up the sampling equipment and then train WWTP staff to operate it. If the working relationship between the two parties is poor, WWTP staff may not be willing to conduct, say, random stratified sampling, which is more difficult than collecting samples over consecutive days.

Another vital aspect of large-scale wastewater sampling is the appropriate handling of both samples and data. Successfully shipping samples to a lab for analysis often depends on courier companies. To ensure that samples arrive on time and in an acceptable state (ideally frozen), it's worth choosing a reputable, trustworthy courier. Furthermore, the volume of sample required, which depends on the difficulty of detecting a particular biomarker, can vary from several microliters to a liter; as such, appropriate freezer space must be available at the analytic labs. Finally, to be able to re-analyze samples for future purposes, careful archiving of instrument data and aliquots of the original samples or extracts of the samples may be necessary. If archiving is not possible at a particular lab, collaboration with other labs may be required. For this reason, data management should be centralized between collaborators, with staff trained to upload quality data in a consistent format, and with dedicated personnel to check data for inconsistencies.

ANALYTIC STRATEGIES FOR DETECTING OPIOIDS IN WASTEWATER

Because opioids are a broad class of substances used both as medical analgesics and as illegal drugs, they present unique complexities related to their detection in wastewater and the interpretation of the resulting data. For instance, heroin itself is normally not detected in wastewater because it's excreted unchanged in very low amounts (Boleda et al. 2007; Postigo et al. 2010; Östman et al. 2014). Instead, the major metabolite of heroin—morphine—is typically analyzed to estimate heroin use. But morphine is also excreted after therapeutic use of either morphine or codeine. Hence, when back-calculating heroin consumption based on morphine concentrations (or "loads") in wastewater, researchers must apply corrections to compensate for a certain amount of the drug being used legally. It is therefore necessary to know the rates of local medical

use of morphine and codeine to be able to subtract the amounts of these substances that were excreted as morphine.

This is the main reason researchers have excluded heroin from annual Europe-wide WBE studies (Thomas et al. 2012; Ort et al. 2014a). It's possible to analyze the minor but exclusive metabolite of heroin, 6-MAM, in WBE studies, but 6-MAM has been found to be unstable in wastewater (Castiglioni 2016) and therefore is barely detectable (Castiglioni et al. 2006; Vuori et al. 2014; Östman et al. 2014). Moreover, the low percentage of excretion of 6-MAM (1.3 percent) can lead to greater uncertainty in the back-calculations. Other heroin metabolites (morphine glucuronides) have also been sought in wastewater but were found to be almost completely reverted to the parent form (morphine) by the β-glucuronidase enzymes of fecal bacteria (Castiglioni et al. 2006).

The main requirements for a WBE biomarker are that it (1) be excreted in consistent amounts in urine, (2) be detectable in urban wastewater, (3) be stable in wastewater, and (4) be a human excretion product for the substance of interest.

OPIOID USE ESTIMATES FROM INTERNATIONAL WBE STUDIES

As mentioned earlier, estimating illicit drug use through WBE requires the analysis and validation of certain biomarkers. The main requirements for a WBE biomarker are that it (1) be excreted in consistent amounts in urine, (2) be detectable in urban wastewater, (3) be stable in wastewater, and (4) be a human excretion product for the substance of interest (Castiglioni and Garcia-Lor 2016). Several opioids have been monitored in urban wastewater so far, and the per capita consumption of some of them was back-calculated using WBE. The opioids and other drugs most frequently investigated are codeine, morphine, heroin and its metabolite (6-MAM), and methadone and its metabolite (2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine, or EDDP), whereas fentanyl, buprenorphine, oxycodone, hydrocodone, and tramadol are less frequent subjects of wastewater studies. Below, we summarize findings related to WBE detection of these opioids across Europe, Australia/New Zealand, and Asia.

Commonly detected opioids: Codeine, morphine, 6-MAM, and methadone

Probably the most abundant opiate in urban wastewater is codeine, which has wide therapeutic use. Concentrations have ranged from 0.1 to 0.2 µg/L in Spain and Croatia (Boleda et al. 2009; Terzic et al. 2010) and were substantially higher in Canada, Sweden, and Finland, ranging from 0.8 to 1.2 µg/L (Yargeau et al. 2014; Vuori et al. 2014; Östman et al. 2014). In Australia, too, wastewater concentrations have been dominated by codeine. Lai et al. (2011) reported that daily mass loads of opioids at an urban Queensland WWTP were three to four times greater than those of morphine—and an order of magnitude higher than methadone and EDDP. And in both Adelaide, Australia (Tscharke et al. 2016), and Auckland, New Zealand (Lai et al. 2017), codeine was one of the most frequently detected substances in wastewater samples, along with morphine and methadone.

Morphine and 6-MAM have been included in all wastewater studies worldwide because they shed light on heroin use. Concentrations in wastewater have varied—from several hundred ng/L for morphine to much lower amounts for 6-MAM. As

noted above, in most WBE studies, researchers have estimated heroin use based on morphine loads, subsequently correcting the amounts by subtracting out any local therapeutic use. When 6-MAM was used instead, the final estimate of heroin use was higher (Table 1). WBE researchers have seen differences in heroin use in different countries, with the highest rates found in the U.K., Belgium, and Croatia and the lowest in Italy and Spain (Table 1). Different patterns of use also emerged across different cities in countries such as Spain and Italy (Zuccato et al. 2016) and over the course of the year in Belgium (van Nuijs et al. 2011). Other recent studies revealed morphine amounts in wastewater equal to 11 to 51 mg a day per 1,000 people in Finland (Vuori et al. 2014) and 50 to 350 mg a day per 1,000 people in Sweden (Östman et al. 2014), but given the low heroin use in these countries, these amounts were attributed almost completely to therapeutic use.

Table 1:
Estimation of heroin use in worldwide wastewater studies

Country (City)	Heroin use (mg/day/1,000 people)	Reference
Italy (Milan)	70	Zuccato et al. (2008)
Switzerland (Lugano)	100	Zuccato et al. (2008)
U.K. (London)	210	Zuccato et al. (2008)
Spain (Catalonia)	138	Boleda et al. (2009)
Spain (Ebro River Basin)	24	Postigo et al. (2010)
Croatia (Zagreb)	262	Terzic et al. (2010)
Belgium (Brussels)	415[a]	van Nuijs et al. (2011)
Italy (17 cities)	60	Zuccato et al. (2016)
Australia (Adelaide)	120[a]	Tscharke et al. (2016)

[a] Calculated using 6-MAM rather than morphine (which required subtracting out estimated amounts due to therapeutic use).

In Asia, researchers have attempted to estimate heroin use using 6-MAM but only found the metabolite in a few samples and at low levels. Their results contradicted epidemiological data that show heroin to be the most used drug in China. This discrepancy could either be the result of the stability issues mentioned previously or the fact that heroin is reportedly the drug of choice in rural, marginalized areas or on the outskirts of urban areas, which were not included in the study (Khan et al. 2014).

In Australia, Tscharke et al. (2016) measured 6-MAM in wastewater samples from Adelaide, South Australia. Their findings indicated few weekly trends and no year-to-year temporal trends over the four-year study. They estimated a daily average use of around 6 doses of heroin per day per 1,000 people (or 40 to 50 doses per week per 1,000 people).

Methadone and EDDP are also frequently measured in WBE studies because they are used to estimate compliance with the substitution therapy for opioid addiction. In some cases, researchers used EDDP to back-calculate methadone use and found spatial differences in countries such as France and China (Nefau et al. 2013; Khan et

al. 2014), although the consumption was stable throughout the week (van Nuijs et al. 2011). Concentrations were normally under 100 ng/L, and EDDP was detected in greater concentrations than methadone (Terzic et al. 2010; Yargeau et al. 2014; Vuori et al. 2014; Östman et al. 2014). However, in wastewater samples from Adelaide, South Australia, Tscharke et al. (2016) found consumption rates of about 100 mg to 150 mg of methadone a day per 1,000 people (equivalent to about eight 100 mg doses a week per 1,000 people), with a noticeable decrease over the last few years. Recent data from wastewater samples collected in New Zealand, which covered about a third of the country's population, suggested average methadone use of about 40 mg a day per 1,000 people (Lai et al. 2017).

Less commonly detected opioids: fentanyl, buprenorphine, oxycodone, hydrocodone, and tramadol

Fentanyl has never been detected in wastewater (Boleda et al. 2009; Östman et al. 2014), probably because it is mostly excreted as a metabolite, norfentanyl. But norfentanyl was detected in all wastewater samples collected during a large monitoring study in Australia, and the amounts increased over the four-year study (Tscharke et al. 2016). Fentanyl is now routinely included in the Australia's ongoing National Wastewater Drug Monitoring Program (O'Brien et al. 2017). The initial results of this program suggest that use of fentanyl and oxycodone may be higher in regional Australia than in the capital cities (O'Brien et al. 2017).

Buprenorphine was not detected in Sweden (Östman et al. 2014), and it was detected only in 3 of 25 locations investigated in France (Nefau et al. 2013). However, it was detected in wastewater in an Australian prison by van Dyken and colleagues (2016), who further compared prescription use of methadone and buprenorphine at the prison and found that, overall, buprenorphine misuse was greater than methadone misuse.

Oxycodone and hydrocodone have been detected more often and in higher concentrations (up to 200 ng/L) in the United States (Chiaia et al. 2008) and in Canada (Yargeau et al. 2014) than in Europe, where concentrations have been less than 20 ng/L (Östman et al. 2014). In Australia, a metabolite of oxycodone (noroxycodone) was frequently found in wastewater, indicating a pattern of use similar to those observed in the United States and Canada (Tscharke et al. 2016). This study also highlighted a large increase in oxycodone use from 2011 to 2015 in Adelaide, South Australia (Tscharke et al. 2016). As with fentanyl, noroxycodone is routinely included in Australia's National Wastewater Drug Monitoring Program (O'Brien et al. 2017).

Tramadol is not typically included in wastewater studies, but when included, it is always detected in untreated wastewater at high levels—for example, in Sweden and Canada (Yargeau et al. 2014; Östman et al. 2014).

COMBINING OPIOID RESULTS FROM WBE WITH OTHER DATA SOURCES

Few studies have compared WBE results for opioids (such as heroin and methadone) with other epidemiological indicators of opioid use. The first-ever WBE study showed

a drop in heroin use in two cities in Northern Italy from 2008 to 2009, which lined up with the decreases in lifetime use and annual use seen in general population surveys over the same period (Zuccato et al. 2011). This decrease could be ascribed to the economic crisis at the time because it was seen mostly with expensive drugs in Italy (cocaine and heroin), whereas the use of cheaper drugs, such as methamphetamine and cannabis, increased. WBE researchers noted further decreases in heroin use in subsequent years (2010 to 2012) in seven large cities in Italy, trends that were once again in agreement with general population surveys (Zuccato et al. 2016). WBE analyses have suggested an increase in heroin use in 2014, but epidemiological data from surveys are not yet available for comparison.

In a study in Lausanne, Switzerland, from 2013 to 2014, researchers compared the estimation of methadone and heroin use in WBE studies with different epidemiological indicators, including general population surveys, syringe distribution programs, and opioid substitution treatment (Been et al. 2015). Methadone use estimated via WBE (based on EDDP) was in agreement with the other indicators. Heroin estimates based on 6-MAM loads were inconsistent, but estimates from morphine loads, combined with prescription and sales data, lined up with figures derived from syringe distribution data and general population surveys. Similarly, in China, Khan et al. (2014) compared methadone estimates from WBE with the amount of methadone used clinically; the results showed that almost all methadone found in sewage comes from clinical use.

Finally, methadone has been a focus of a number of studies in Australia and a recent study in Auckland, New Zealand. Lai et al. (2017) estimated that an urban community was using about 20 mg a day per 1,000 people, which lined up reasonably well with data on prescription use (13 mg a day per 1,000 people). It is further noteworthy that both Lai et al. (2011), who studied the general population, and van Dyken et al. (2016), who studied a prison population, found fairly good accord between the prescription of methadone and the estimated use based on wastewater analysis. Tscharke et al. (2016) noted that an increase in oxycodone use observed using WBE between 2011 and 2015 corresponds with a rise in the misuse of pharmaceuticals identified in survey data.

Together, these studies show that combining different sources of data strengthens the results from WBE and that WBE can be a reliable indicator of opioid use in a community, providing realistic and timely estimates of use trends.

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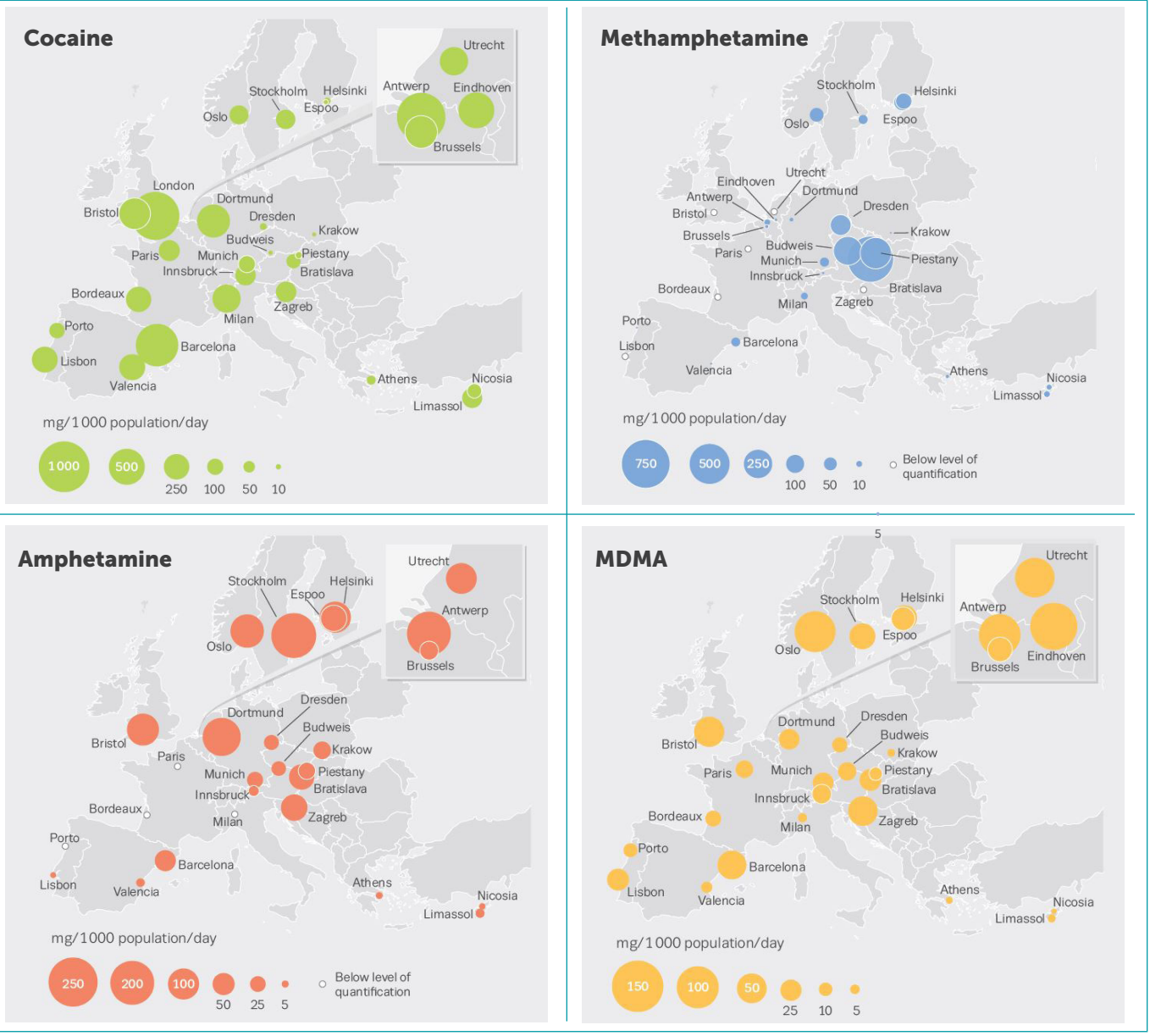
WBE AND DRUG SURVEILLANCE IN EUROPE: LESSONS LEARNED

EMCDDA is an agency of the European Union (EU) that collects, analyzes, and disseminates information on drug use for policy makers and practitioners across Europe. Together with partners organizations in the EU (Europol and the European Medicines Agency) and national monitoring centers, EMCDDA operates the EU early warning system on new psychoactive substances. Data collected through this system is combined with data from national partners and European research networks and to feed into a multi-indicator and multisource drug surveillance system in Europe.

In 2016, EMCDDA released findings from wastewater monitoring from over 60 cities (Figure 2), including data from SCORE's 2016 monitoring exercise.[12] This release not only underscored the fact that WBE is now an accepted part of the European drug-monitoring system but also showed the potential of WBE to provide more timely information than many other data sources. Given the increasingly dynamic nature of modern drug abuse, WBE is particularly valuable as a leading-edge indicator of new trends. For example, the most recent wastewater data suggest that cocaine is becoming more available around Europe, but it will be one to three years before data on this topic are compiled and analyzed from other routine sources.

Figure 2:
Geographic patterns of drug use across European cities



[12] For a summary of the findings, visit http://www.emcdda.europa.eu/topics/pods/waste-water-analysis#panel2.

Europe was an early adopter of WBE; EMCDDA held its first technical meeting on WBE in April 2007 and began routinely collecting data in 2011. At the time of the first meeting, WBE was not only novel, but there was major political and technical opposition to it. Europe's eventual incorporation of WBE into routine monitoring of drug trends may provide some important lessons for the use of this method elsewhere. Below, we summarize the seven most important lessons learned:

1) **Recognize WBE as a complementary approach and foster multidisciplinary partnerships.** Many methods and data sources have been developed to estimate and describe drug use and its associated health and social outcomes. Each source highlights a certain aspect of the complex drug phenomenon, but all (including WBE) have their limitations. The findings from WBE are therefore more useful when combined with data from other sources. Because the scientific disciplines of WBE researchers are often very different from those of researchers in more traditional areas of drug surveillance, there is a need for partnership and communication across different disciplines. Wastewater analysis is a powerful new tool in the epidemiological toolkit for drug use research, but it is one that adds to, rather than replaces, existing approaches.

2) **Understand and communicate the strengths and limits of WBE.** WBE is a complex method with strengths and weaknesses that have, at times, been both over- and understated. It has clear advantages in terms of reporting trends in real time and reducing problems associated with response bias and self-reports. But it's also limited in its capacity to estimate the prevalence of drug use, and there are knowledge gaps in areas that inform WBE estimation (for example, the behavior of some biomarkers in the sewer system or the ways in which humans metabolize and excrete different drugs). Both policy and technical audiences need to know that WBE is a valuable complementary tool that has limitations—some of which can be addressed by future work, but some of which are intrinsic to the approach (EMCDDA 2016). Clear and accurate communication about these details has been essential to incorporating WBE into the European surveillance system.

3) **Invest in methodological development and standards for WBE.** Researchers have convinced policymakers in the European Union that WBE has considerable potential—if it can be developed appropriately. As a result, policymakers made funds available to address important methodological issues, support training and capacity development, and establish standards, many of which now have international relevance. As different countries adopted WBE, it became necessary to establish practical guidelines to ensure the proper use of the approach, as described previously. The guidelines have been important for developing the potential of WBE and have also helped convince those initially skeptical about the scientific robustness of the method that due consideration was being given to data quality.

4) **Convey findings carefully.** The complexity of WBE means that study teams must carefully and appropriately disseminate results to different audiences. The importance of this is illustrated by an early experimental study of a small Spanish town. Inappropriate reporting wrongly suggested that the town had some of the highest rates of cocaine use in the world, which for a time led to major political opposition to WBE. Researchers must recognize that WBE is still in a development phase and that results from the approach can be difficult for nontechnical audiences to understand. Researchers must carefully interpret wastewater data; put findings in the proper context; and communicate them clearly to institutional stakeholders, the public, and the media. Otherwise, the misinterpretation or misuse of WBE data could undermine adoption of the method.

5) **Know the difference between using WBE for epidemiological surveillance, monitoring, and research versus more operational uses.** In the United States and Europe, opponents of WBE have raised concerns about personal privacy or the risk of test results being used inappropriately. Some of these issues can be addressed by adhering to an ethical framework (see Lesson 6 below). But the European experience also strongly suggests the need for conceptual clarity and distance between use of WBE for research purposes versus for law enforcement, occupational surveillance, or other such purposes.

6) **Develop an appropriate ethical framework.** As with any research method, adhering to ethical standards is a must for earning public acceptance. Initial concerns about WBE focused on the issue of informed consent, but the public has now generally accepted that once a wastewater sample has sufficiently mixed with others, there is no need to get consent from donors. But other ethical issues have emerged, such as the targeting of specific populations. Wastewater testing has occasionally been used to measure drug use in small communities, including workplaces, schools, prisons, neighborhoods, and crowds at music festivals (Hall et al. 2012). This can involve ethical risks, including identifying a particular group within the community, stigmatizing a group, and harming a business economically. In 2016, ethical guidelines for WBE were published to help mitigate these risks (Prichard et al. 2014).

7) **Recognize the trade-offs of focusing on nonrepresentative geographic areas.** In Europe, researchers have made many comparisons at the country level. But for the most part, WBE data have only been available for a nonrandom selection of cities, and these cities are not necessarily representative of countries as a whole. Thus, although detailed geographic data on drug use are available from cities, these data do not necessarily reflect trends at the national level.

CONCLUSIONS

The WBE approach has improved considerably in recent years. This is mainly due to strong collaboration between research groups all over the world, which has enabled the use of a best-practices protocol and has improved the integration of findings into the evidence base. Cooperation has been key to improving research in this new field of study and will continue to be important as new organizations or institutions begin wastewater-based research in other countries.

Because of the multidisciplinary nature of this emerging field—involving both environmental and social sciences—another key challenge is to merge different types of knowledge from epidemiologists, analytical and environmental chemists, environmental engineers, pharmacologists, toxicologists, experts in forensics, and stakeholders from the public-health sector (such as addiction and prevention institutions). A multidisciplinary partnership will enormously enhance the potential of WBE to complement and enrich the panel of information available from epidemiological studies.

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APPENDIX A: SYMPOSIUM PARTICIPANT LIST

Table A.1 lists individuals who participated in the symposium in Washington, DC. The meeting was also streamed through a webinar and engaged virtual participants (not listed) through live polling.

Table 1:
Symposium Participant List

Stakeholder group	Institution	Representative
Federal government	High-Intensity Drug-Trafficking Area Program	J. Beeson
Federal government	National Governors Association	J. Locke
Federal government	National Institute on Drug Abuse	M. O'Brien
Federal government	Office of National Drug Control Policy	T. Zobeck
Federal government	Office of the Assistant Secretary for Planning and Evaluation	C. Jones
Federal government	Substance Abuse and Mental Health Services Administration	M. Campopiano
Federal government	Substance Abuse and Mental Health Services Administration	J. Fan
Federal government	U.S. Senate	D. Christie
Federal government	U.S. Senate	A. Hoyos
State/local government	Association of State and Territorial Health Officials	K.T. Kramer
State/local government	Association of State and Territorial Health Officials	N. Porter
State/local government	Governing magazine	J.B. Wogan
State/local government	National Association of Counties	J. Moran
Public health	American Society of Addiction Medicine	A. Zgierska
Public health	Association of Public Health Laboratories	J. Nassif
Public health	Columbia University	L. Vaezazizi
Public health	Governing magazine	M. Quinn
Public health	Johns Hopkins University	M. Fishman
Public health	Johns Hopkins University	R. Johnson
Public health	National Association of State Alcohol and Drug Abuse	R. Harwood
Public health	National Institute of Standards and Technology	K. Lippa
Public health	Tennessee Department of Health	M. McPheeters
Public health	United Rheumatology	J. Glaudemans
Public health	University of Kentucky	G. Mays
Public health	Vanderbilt University	S. Patrick
Public safety	New Jersey State Police	J. Colon
Public safety	Urban Institute	N. La Vigne
Public safety	Urban Institute	D. McClure
Environmental issues	American Water	R. Marfil-Vega
Environmental issues	Hampton Roads Sanitation District	J. Pletl
Environmental issues	Tufts University	N. Wilton
Wastewater research	European Monitoring Centre for Drugs and Drug Addiction	L. VanDam
Wastewater research	Hofstra University	K. Bisceglia
Wastewater research	Murray State University	B. Subedi
Wastewater research	Puget Sound University	D. Burgard
Wastewater research	University of Antwerp	F. Been
Wastewater research	University of Queensland	J. Mueller
Wastewater research	University of Washington	C. Banta-Green
Evidence-based research	Laura and John Arnold Foundation	J. Williams
Evidence-based research	Mathematica Policy Research	A. Keshaviah
Evidence-based research	Mathematica Policy Research	A. Logie
Evidence-based research	Mathematica Policy Research	C. Ferro
Evidence-based research	Mathematica Policy Research	C. Thornton
Evidence-based research	Mathematica Policy Research	J. de Vallance
Evidence-based research	Mathematica Policy Research	M. Stagner
Evidence-based research	Mathematica Policy Research	R. Goyal
Evidence-based research	Mathematica Policy Research	S. Bruns
Evidence-based research	MITRE Corporation	J. Tripathi
Evidence-based research	Project Evident	S. Cody

APPENDIX B: OPIOID AND SUBSTANCE ABUSE DATA SOURCES

Figure B.1 lists the datasets used by key stakeholders working in opioid and substance abuse, as reported on the symposium participant survey administered by Mathematica.

Figure B1:
Datasets used by key stakeholders

Treatment or prescription data

- ASSIST
- CMS claims
- CMS prescriptions
- DEA CSAT
- EMCDDA
- EHR data
- HCUP
- IMS Health
- Local-level self-reporting data
- Medicaid claims records
- MMWR from CDC
- Naloxone from first responders
- NSDUH
- N-SSATS
- ME office overdose data
- (State) PDMP
- State child welfare data
- State hospital & ED discharge data
- State Medicaid drug utilization data
- State-level medical claims data
- State sales data
- TEDS
- NYS OASAS treatment admissions

Law enforcement data

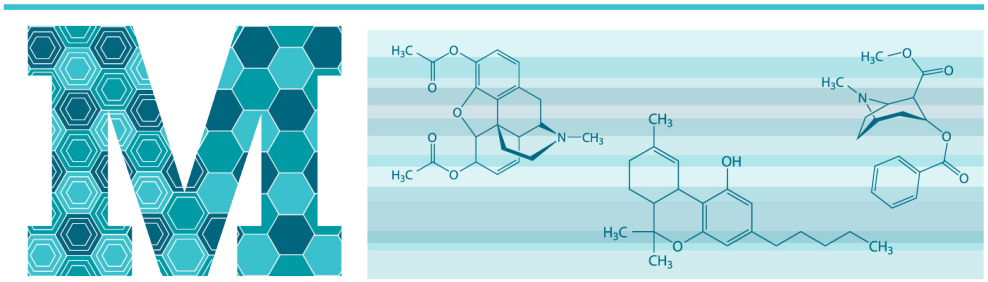
- ACIC data
- DEA ARCOS
- EMCDDA
- EMS
- Local police data
- N-DEx
- NFLIS
- NIBRS
- NYS DCJS arrest data
- State department of corrections, arrests, and conviction data

Other data

- AddHealth
- CDC WONDER
- Data from county
- DRID
- EMCDDA
- Euro-DEN
- General population surveys
- Medical records
- MEPS
- MTF
- NAPHSIS
- PDU
- Published studies
- Statewide hospital discharges
- Trendspotting studies
- Vital records and statistics
- Wastewater data
- YRBS

Acronyms and Abbreviations

ACIC: Australian Criminal Intelligence Commission
AddHealth: National Longitudinal Study of Adolescent to Adult Health
ARCOS: Automation of Reports and Consolidated Orders System
ASSIST: Alcohol, Smoking, and Substance Involvement Screening Test
CDC: Centers for Disease Control and Prevention
CMS: Centers for Medicare & Medicaid Services
CSAT: Center for Substance Abuse Treatment
DEA: Drug Enforcement Administration
DCJS: Division of Criminal Justice Services
DRID: Drug-related infectious diseases
ED: Emergency department
EHR: Electronic health record
EMCDDA: European Monitoring Centre for Drugs and Drug Addiction
EMS: Emergency medical services
Euro-DEN: European Drug Emergencies Network
HCUP: Healthcare Cost and Utilization Project
ME: Medical examiner
MEPS: Medical Expenditure Panel Survey
MMWR: Morbidity and Mortality Weekly Report
MTF: Monitoring the Future
NAPHSIS: National Association for Public Health Statistics and Information Systems
N-DEx: National Data Exchange
NFLIS: National Forensic Laboratory Information System
NIBRS: National Incident-Based Reporting System
NSDUH: National Survey on Drug Use and Health
N-SSATS: National Survey of Substance Abuse Treatment Services
NYS: New York State
OASAS: Office of Alcoholism and Substance Abuse Services
P(D)MP: Prescription (Drug) Monitoring Program
PDU: Problem drug use
TEDS: Treatment Episode Data Set
WONDER: Wide-Ranging Online Data for Epidemiologic Research
YRBS: Youth Risk Behavior Surveillance System



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