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Invited Commentary

Invited Commentary: Drug Checking for Novel Insights Into the Unregulated Drug Supply

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Tobias et al. (*Am J Epidemiol*. 2022;191(2):241–247) present a novel analysis of time trends in fentanyl concentrations in the unregulated drug supply in British Columbia, Canada. The preexisting knowledge about unregulated drugs had come from law-enforcement seizures and postmortem toxicology. As both of these data sources are subject to selection bias, large-scale drug-checking programs are poised to be a crucial component of the public health response to the unrelenting increase in overdose in North America. As programs expand, we offer 2 guiding principles. First, the primary purpose of these programs is to deliver timely results to people who use drugs to mitigate health risks. Second, innovation is needed to go beyond criminal justice paradigms in laboratory analysis for a more nuanced understanding of health concerns. We provide examples of the role adulterants play in our understanding of drug harms. We also describe the applications and limitations of common laboratory assays, with implications for epidemiologic surveillance. While the research and direct service teams in British Columbia have taken groundbreaking steps, there is still a need to establish best practices for communicating results to sample donors in an approachable yet nonalarmist tone.

drug checking; fentanyl; harm reduction; opioids; public health surveillance; substance use

Abbreviation: FTIR, Fourier-transform infrared.

Editor's note: *The opinions expressed in this article are those of the authors and do not necessarily reflect the views of the* American Journal of Epidemiology.

In this issue of the *Journal*, Tobias et al. (1) present an innovative analysis of time trends in the concentration of fentanyl in the unregulated drug supply in British Columbia, Canada. We applaud the authors for both the life-saving program they implemented and their report of fluctuations in "heroin" purity. While uncertainty in fentanyl concentrations has long been supported by anecdotal community reports, this analysis provides a rare quantification of unregulated drug market time trends. In contrast to previous studies (2, 3), Tobias et al. do not rely on law-enforcement seizure samples, which are subject to undefined selection effects. Instead, using data from a well-established community-based drug-checking program, they report a slight decreasing trend in the median and variance of fentanyl concentrations over a 26-month period but also note a possible cyclical pattern.

PUBLIC HEALTH CONTEXT

Historically, public health knowledge about unregulated drug composition has been limited by entrenched data collection paradigms. Most information originates from postmortem and clinical toxicology, law-enforcement seizures, drug-treatment program enrollees, and qualitative field studies (4). These data sources emphasize the most extreme consequences of drug use and do not accurately represent routine drug exposure (5, 6). General population surveys are often slow to adopt new measures and are plagued by selective nonresponse (7–9). Law enforcement seizure data are used primarily in criminal prosecutions and therefore do not have a health-relevant sampling frame; they also

take years to be made public and are reported using overly simplistic frequency tables (10). While useful for epidemiologic analyses, the collective design flaw is that existing data systems do not provide information to people who use drugs in a timely and actionable manner to prevent harm. Tobias et al. improve upon this situation substantially. They describe an approach that uses field testing to return real-time results to participants, paired with subsequent laboratory testing and statistical modeling that generates more robust surveillance insights.

In North America, the dozen spectroscopic drug-checking services currently operating are located within organizations that provide health and social services. Samples are brought in by participants who use results to make informed choices. Some programs also test drug litter and discarded samples found by law enforcement. Point-of-care testing using Fourier-transform infrared (FTIR) spectroscopy takes about 10–20 minutes. Spectroscopic results are interpreted by technicians and summarized in terms of content and relative abundance (e.g., "This sample contains a moderate amount of fentanyl and is cut with lactose and the artificial sweetener inositol").

Drug checking has been shown to be acceptable to community members (11, 12). While locations in North America are beginning to expand drug checking, this type of service has been long used in music festival and community settings in Canada, Australia, and Europe, particularly in the Netherlands and Spain (13–22). In the United States, drug checking dates back to the 1970s, with subsequent expansion through harm reduction organizations such as DanceSafe in the 1990s (23). The analysis from British Columbia is the largest study of its type conducted in North America. The study also heralds a progression from disposable test strips (24, 25) that dichotomously detect a single substance to infrared spectroscopy, which can assay molecular mixtures. The analysis by Tobias et al. also stands out because fluctuations in potency are a key driver of overdose (4); risk of respiratory depression increases when doses are more potent than expected. Therefore, this analysis represents a powerful and emerging surveillance paradigm for monitoring the unregulated drug supply.

TWO GUIDING PRINCIPLES

Large-scale drug-checking programs are increasingly recognized as an innovative and necessary component of the public health response to the unrelenting increase in overdose in North America (26, 27). They have recently been recommended by the US Centers for Disease Control and Prevention (28). We offer 2 guiding principles for new drug-checking programs.

First and foremost, the program's primary purpose should be to deliver results in a timely manner to people who use drugs to empower behavior change. At a music festival in the United Kingdom (29), 1 in 5 users disposed of their substances after receiving unfavorable test results. In another study, two-thirds disposed of drugs after learning that they were sold something other than what was expected (30). These findings may seem to be at odds with clinical and social work experience but are explained with attention to the sampling frame. Data collected from substance-abuse treatment centers come from those who are seeking help for problematic drug use. During severe substance use disorder, the need to stave off withdrawal may lead to less discriminating consumption, what economists term inelastic demand (31, 32). In contrast, syringe services (33, 34) and drug-checking programs (35) represent a wider spectrum of substance use, including those without diagnosed "disorders" and occasional drug users who submit samples for friends based on altruistic motivations (36, 37). As explained by the elaboration likelihood model of persuasion (38), people with less compulsive use will employ rational decision making and are therefore more amenable to information-based messaging (39). On an applied level, syringe service program staff know that there are times when a participant will be interested in informational pamphlets and other unreceptive moments when survival needs take precedence (35).

The second principle is expanding beyond preexisting paradigms in analytical chemistry. Over the past 5 years, laboratory impurity detection methods have focused on isolating analogs of fentanyl and methamphetamine recently placed on prohibited substance lists; the intent is to increase criminal prosecution (40, 41). To apply these technologies in public health requires innovation; new laboratory chemistry methods may be required to identify harmful adulterants that would not be detected with existing confirmatory testing protocols, such as derivatization to detect sugars (common cutting agents) that might otherwise be vaporized in traditional gas chromatography. While the concern over fentanyl in the unregulated supply is warranted, other adulterants have implications for health. The veterinary anesthetic xylazine is increasingly appearing in overdose fatalities (42, 43) and may cause atypical ulcers beyond the injection site (44, 45). Phenacetin, caffeine, etizolam, and synthetic cannabinoids are also increasingly used as adulterants (46, 47). In North Carolina, we detected niacin (which can cause severe flushing) in heroin-fentanyl samples, revealing that there is much we do not yet understand. As the authors from British Columbia have done elsewhere (48), we encourage public health-oriented drug-checking services to look beyond controlled substances and report other adulterants. At a time when the variety of substances in unregulated drugs is proliferating, granular information on composition can guide clinicians to more precise diagnoses and timely care.

METHODOLOGICAL CONSIDERATIONS

Tobias et al. offer a welcome reminder of, and potential solution to, methodological barriers we face in the study of unregulated drugs. Yet, there is room for epidemiologic and statistical innovation beyond temporal smoothing that they employed.

The primary method used by Tobias et al. was FTIR spectroscopy. A continuous range of infrared light is directed through the sample, and different molecular configurations interrupt and scatter the light in predictable manners. The software used for quantitative analysis, OPUS (Bruker,

Billerica, Massachusetts), uses algorithms to convert spectral intensity to estimated relative concentrations. This spectroscopic method is not as precise as quantitative nuclear magnetic resonance, as FTIR can miss fentanyl in low concentrations (49, 50). FTIR also has low power to discriminate between closely related fentanyl analogs, but animal models suggest that analogs may have differential pharmacologic pathways (51). Confirmatory testing, for example with liquid and/or gas phase chromatography, is therefore critical for accuracy. There is a level of subjective interpretation engendered in analyzing FTIR spectra, without an established lexicon to express that uncertainty. Therefore, the idealized practice is to use fentanyl test strips, then FTIR, and follow-up with confirmatory testing, which Tobias et al. did. The authors acknowledged that confirmatory testing was a referral-based process and conducted on a nonrandom subset of samples, potentially resulting in selection bias that favors observation of unexpected or aberrant samples. They did not discuss the confirmatory testing results, however. As drug-checking services expand, they may intentionally or unintentionally attract different clientele. Reporting consistency in participant characteristics over time could increase the credibility of trend analyses. Although these limitations exist, this paper still represents a significant contribution to the fields of harm reduction and epidemiology.

In terms of generalizability, the authors acknowledge that these data may not be representative of all drug samples in British Columbia. These data were samples from people who sought drug-checking services at several community-based organizations. People not involved in these community services may obtain drugs from other sources. Thus, being voluntary programs, their representativeness is unknown. This issue has been discussed at length during monthly deliberations in the community of practice (the Alliance for Collaborative Drug Checking). Across North America, there is a general sense that the preponderance of samples are submitted by people who use drugs who are of White race, perhaps reflecting service provider catchment areas. We cannot preclude the possibility that drug-checking services may currently miss or underrepresent drugs circulating in communities of color.

Issues with generalizability of drug-checking data have the potential to be assessed through external validation. For example, drug-checking services in the Netherlands have shown strong concordance across forensic settings, consumer samples, and poison centers (52). When combined with participant demographics, these types of analyses can lay the groundwork for characterizing the generalizability of drug-checking services.

The emphasis on molecular detection also carries the risk of what we call the "tyranny of the molecule": the cognitive bias that confers primacy to molecular information. Recent discussions in the Alliance for Collaborative Drug Checking indicate complex decision-making by participants beyond opioid potency alone. Especially in the presence of adulterants, our collective field experience suggests that subjective accounts and contextual details are as crucial as biomolecular assays. In line with suggestions from qualitative researchers (53), Alliance members have begun to document experiential and euphorigenic batch profiles. These phenotypes may empower participants to discriminate between samples during purchasing, an extension of established behavior (54). Contextual information, including physical descriptions, distribution locations, and unique packaging, provide cues that can be used to avoid troublesome batches. As drug-checking programs expand, we therefore encourage a repositioning that treats molecular and subjective experience data equally.

RESEARCH NEEDS

Research is needed on how to best present information to participants (55). Anecdotal concerns are routinely raised that high-potency warnings may attract risk-takers. However, our experience has been that people who use drugs have heterogeneous health behaviors, but many are informed consumers who actively try to protect their health (56). Research on communicating potency and adulterant alerts is needed through formal message-testing frameworks (57). At a program level, understanding pre-test probabilities for confirmatory testing would also help statistical model selection. At an individual level, motivations and demographics of participants in drug-checking services could also be elucidated.

While the research and direct service teams in British Columbia have taken groundbreaking steps, only a few other locations in Canada have drug-checking programs, the other most mature being in Toronto (58). In the United States, only a handful of spectroscopy-based drug-checking programs currently operate. Therefore, drug checking is regarded as experimental and is excluded from "evidence-based" policy directives. At the same time, the assumed efficacy of law-enforcement interdiction on the drug supply is rarely questioned. In a period where the unregulated drug supply is highly unpredictable (59), high-quality empirical studies situating drug checking are needed urgently to generate the evidence base for this emerging intervention.

CONCLUSIONS

There are no simple answers to current problems with unregulated opioids in North America (60), and drug-checking programs are but one component of comprehensive drug information surveillance (61). Drug-checking programs are the first line of public health defense against drug cartels. To realize their potential to prevent health harms, epidemiologic attention and methods experimentation are urgently needed.

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