Clinical Toxicology (2009) **47**, 573–579

ISSN: 1556-3650 print / 1556-9519 online
DOI: 10.1080/15563650902967404

informa
healthcare

ARTICLE

Real-time surveillance of illicit drug overdoses using poison center data

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Background. In early 2006, government and media sources reported that crime syndicates were mixing fentanyl with heroin. This was followed by an increase in heroin overdoses and opiate-related deaths. The most recent fentanyl outbreak illustrated the need for identifying and establishing effective and responsive real-time surveillance tools to monitor drug overdoses in the United States. *Objective.* In this study, poison call center data from Illinois were evaluated to determine whether the data could have detected the outbreak that occurred in Illinois in early 2006 and whether it could be used for real-time surveillance. *Methods.* For this analysis, a two-step approach was used to analyze potential heroin-related calls. First, the data were analyzed retrospectively to identify whether any significant temporal shifts occurred, then a prospective analysis was conducted to simulate real-time surveillance. *Results.* Between 2002 and 2007, there were a total of 1,565 potential heroin-related calls, and the calls increased by 63.6% in 2006 compared to 2005. In the prospective analysis, the principal model would have identified the outbreak in March 2006. *Conclusions.* If there had been a real-time surveillance program using poison center data, the outbreak would have been identified 1 month before the initial postmortem reports to the Centers for Disease Control and Prevention at the end of April 2006. Poison center data provide the potential for an earlier warning system than postmortem data sources, because the reports are usually made within hours of the exposure. Poison center data can be effectively used to monitor heroin-related exposures.

Keywords Heroin; Fentanyl; Drug overdose; Surveillance; Real time; Poison center

Introduction

Toward the end of 2005 and early 2006, reports came out that crime syndicates were mixing fentanyl with heroin.[1–4] This was followed by confirmed reports of an increase in heroin overdoses and opiate-related deaths from medical examiners.[5] The largest number of reported deaths occurred in Chicago.[5] Fentanyl is an opiate with a far lower effective dose and lethal dose than heroin. In opiate-naïve individuals, the minimum lethal dose of heroin has been reported to be as low as 10 mg[6–8] compared to approximately 0.25 mg for fentanyl.[8,9] There are various fentanyl analogues found in street drugs, but the most commonly reported analogues are α-methylfentanyl and 3-methylfentanyl.[10]

This was not the first time drugs mixed with fentanyl were sold on the street. The first documented report of fatal overdoses of an illicit fentanyl analogue in the United States occurred in Orange County, CA, in 1979.[10] This was followed in 1984 by the first documented mass outbreak of fentanyl overdoses, which also occurred in California.[10,11] During the period of 1980–1988, the California lab responsible for following the outbreak identified 112 overdoses because of exposures to 10 different illicit fentanyl analogues.[11] Later in the 1980s and through the 1990s, there were other reports of outbreaks of fatal fentanyl overdoses occurring in Pittsburgh, PA,[12] Minneapolis, MN,[13] and Patterson, NJ.[14] Overdoses from fentanyl abuse have also been reported in Finland and Russia.[15]

The most recent fentanyl outbreak illustrated the need for identifying and establishing effective and responsive real-time surveillance tools to monitor drug overdoses in the United States.[5] All previous reports of fentanyl overdoses in the United States have relied upon postmortem data. Although information about deaths is important, there is a greater reporting lag between the overdose event and the postmortem confirmation compared to other data sources that gather information on patients while they are usually still alive – including poison center data. Public health investigators may be able to detect events earlier using poison center data because calls are generally made within hours of the time of the overdose by the patient, EMS personnel, or hospital staff. In this study, poison call center data from Illinois were evaluated to determine whether the data could have detected the outbreak that occurred in Illinois in early 2006 and whether it could be used for real-time surveillance. In addition, different statistical approaches for identifying the outbreak were evaluated.

Received 2 December 2008; accepted 13 April 2009.
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Methods

Data source and case definition

The Illinois Poison Center (IPC) provided a complete data set of all calls made to IPC between 2002 and 2007. Trained nurses, pharmacists, and physicians receive the phone calls and provide the caller with poison prevention and management information. The IPC staff is trained in the data entry protocols and provides a wide range of information about the exposed person including demographic information, reported source of exposure, and treatment follow-up.

The IPC staff identifies exposure sources using a variety of information, including patient self-reports (i.e., nonmedical caller), history provided by the patient to medical personnel, physical examination findings reported by health-care providers, and emergency medical personnel description of the scene such as signs, symptoms, and physical evidence (e.g., needles and needle marks on extremities). The principal assessment of exposure is made using a toxidrome, which is a constellation of symptoms that are consistent with a poisoning. In this case, the opioid toxidrome is lethargy, miosis, and decreased respiratory rate.

In this analysis the following two case definitions were used:

1. *Heroin-related exposures*: The first case definition called "heroin-related exposures" was broadly defined and included exposure to heroin, methadone, and "other/unknown opioids." Methadone was included because it is a frequent treatment for heroin addiction and may be misrepresented as the source of exposure because the individual may be reserved about admitting to using heroin. The other/unknown opioids category includes fentanyl; therefore, it was included in this case definition. It is plausible that an informed medical professional suspected fentanyl tampering in an exposed individual once reports began to surface about the mixing of fentanyl with heroin.
2. *Heroin-only exposures*: The second case definition was more narrowly defined and included only heroin-specific exposures.

To evaluate the quality of the coding for the exposures, a random sample of 50 cases was drawn from the first case definition of heroin-related exposures. The detailed case profiles were assessed for the random sample. These case profiles contain a level of detail not available in the data set, including narratives. Among those sampled, 29 cases were treated at a health-care facility, of which 86% were administered naloxone, an opioid receptor competitive antagonist. Of the four who did not receive naloxone, the treating physician felt that it was not necessary because the exposure was of a low dose. The 21 cases not treated at a health-care facility included individuals calling from their home, refusing medical attention, or persons who left the health-care facility against medical advice. In the same random sample, the exposure category (i.e., heroin, methadone, and unknown/other opioids) matched the detailed description of exposure in the case file for every case.

Statistical approach

For this analysis, a two-step approach was used to analyze the data. First, the data were analyzed retrospectively to identify significant temporal shifts between January 2002 and December 2007 (i.e., clusters). Second, we analyzed the data prospectively by truncating the data to the time period before the known cluster and then adding in data incrementally until the cluster was identified prospectively. For the retrospective analysis, the Chow statistic and the scan statistic were used to identify anomalous periods or surges in the call volume. For the prospective analysis, three different methods were compared: cumulative sum (CUSUM) modeling of the residuals, Pulse Analysis (PULSAR) method, and autoregressive integrated moving average (ARIMA) model. Both the time-series models and the cluster analyses provided information on the frequency and type of outbreaks observed in the state of Illinois since the year 2002.

Step 1: retrospective analysis

The initial step to the procedure was to analyze the data for significant temporal shifts in heroin exposures based on the actual time-series data. Were there any significant outbreaks between 2002 and 2007? The data were analyzed by monthly calls.

Scan statistic

The scan statistic is a statistical technique used to determine whether an observed increase in cases in a given period of time is statistically significant.[16] SatScan (v.7.0.3, Martin Kuldorff of Harvard Medical School and Information Management Services Inc., Silver Spring, MD, USA) was used for the temporal scan statistic. A Poisson distribution was used for the model.[17]

Chow test

The Chow test is used as part of an autoregression model. Autoregression models (PROC AUTOREG) allow for modeling autocorrelation of the error term. After autocorrelation is accounted for in a model, the Chow test is used to identify significant temporal shifts (i.e., break points, joinpoints, and elbows) in the data. The Chow test achieves this by dividing the data into two segments: one before and one after the break of interest. The null hypothesis is that the slope of segments one and two are equal. The Chow test is an F-test based on the residual sum of squares (SSE) derived from the two segments and a restricted SSE.[18] The restricted SSE is based on a variation of a linear regression model using the residuals from the complete series. SAS (v9.1, SAS Institute Inc., Cary, NC, USA) software package was used for both the autoregression models and the Chow test.

Step 2: prospective analysis

If an outbreak was identified retrospectively, then a prospective analysis was conducted to determine when the outbreak would have been identified if the data were being analyzed in real time. This prospective approach also provides us with the number of false positives that would have occurred if the analyses were conducted in real time, in addition to a critical value or threshold for setting future real-time alerts. The general method for the prospective analysis is to truncate the time series to include only observations occurring prior to the initial outbreak identified in the retrospective analysis. Based on the retrospective analysis, the data were truncated to December 2005. Therefore, the starting point for the prospective analysis included data from January 2002 through December 2005. Then calls occurring in a single unit of time are added to the time series, and the data are analyzed. The series is extended incrementally by one unit of time until the outbreak is identified. The point at which the outbreak is identified represents the earliest point in time that the outbreak would have been identified in a real-time analysis using a given model. However, because the truncated data are not influenced by the outbreak, smaller events may be statistically significant and produce false positives prior to the principal cluster. In the prospective analysis, the following statistical procedures were used: CUSUM recursive residual plot analysis, PULSAR method, and ARIMA models.

CUSUM

The CUSUM method sums the difference between observed and expected counts during a given period.[19] An anomaly or temporal shift occurs when cumulated observed counts exceed the upper bound of the expected values. The strength of CUSUM is that it is capable of detecting smaller shifts from the mean than other statistical methods, and it detects these shifts more quickly. In addition, the residuals can be calculated with an autoregression model, which takes autocorrelation into account. Based on the output from the autoregression model, the recursive residuals are plotted to determine the point of a break when the exact date is not known. Recursive residuals are a linear transformation of ordinary residuals.[20] A break is indicated when the plotted residuals wander outside the confidence intervals on the CUSUMSQ plots. SAS (v9.1, SAS Institute Inc.) was used for the Poisson CUSUM analysis.[21,22]

LOESS/PULSAR

First, a baseline is defined for the time series by smoothing the series using locally weighted scatterplot smoothing (LOWESS or LOESS).[23,24] The LOESS procedure can be used for a variety of data sources because the model does not make the assumptions of ordinary linear regression such as normality and independence. Another key benefit of using LOESS modeling is that the iterative weighting procedure provides robust estimates especially when the series has outliers. Generally, LOESS works by fitting models to subsets of the data. The estimation of these subsets is done with weighted least squares, in which larger weights are given to points nearest the estimated response and lower weights to points further away. The data from the multiple subsets across each data point are used to describe the variation in the series. The user can define the weights to be used in the model. We selected the smoothing parameter (weight) based on the model that minimized the Akaike's information criterion, which reflects model fit and complexity. For the PULSAR analysis, residuals are then calculated from the observed values minus the smoothed LOESS estimates. These residuals are then standardized to derive a series of scaled residuals. Peaks are then identified in the series as described by Merriam and Wachter (1982).[25] For the PULSAR analysis, we used PC-PULSAR software.[26] The following G-parameters corresponding to a 1% false detection rate were used as presented by Merriam and Wachter[25]: G(1), 4.40; G(2), 2.60; G(3), 1.92; G(4), 1.46; G(5), 1.13.

ARIMA

The final prospective tool used was an ARIMA time-series model. Because each data series has a unique structure, ARIMA models are developed empirically for each dependent variable using a three-stage iterative process: identification, estimation, and diagnosis. Identification involves analysis of the crude series to determine stationarity. The Dickey–Fuller test (*D–F* statistic) and structure of the autocorrelation function and partial autocorrelation function were used to determine stationarity. If a series is not stationary, we differentiate the data to achieve stationarity. Estimation involves defining the autoregressive and moving average filters. The following diagnostic procedures were used: (1) the autocorrelation function and partial autocorrelation function of the residuals to determine whether the structure in a series has been accounted for, (2) modified Box–Ljung *Q*-statistic to further evaluate whether structure remains in the series, (3) Hessian matrix to assess collinearity, (4) and the Hinich test to assess whether the series is linear. Based on the Hinich test and the appropriateness of the fitted ARIMA models, we did not transform any of the data series or use nonlinear models (e.g., MARS). SAS (v9.1, SAS Institute Inc.) software package was used for all ARIMA analyses.

Threshold values

Based on the ARIMA models used in the prospective analyses, the threshold of the alert was defined. Many researchers use 3 SD as a threshold,[27] but depending on the sensitivity desired, the thresholds can vary from 1 to 3 SD. In this analysis, the upper 95% bounds were used for determining the threshold values. The threshold value represents the number of calls in which a significant deviation from the baseline has occurred.

Results

During the 6 years of available data, there was a total of 1,565 heroin-related calls, according to the broader first case definition (Fig. 1). The largest proportion was identified as other/unknown opioids (45.6%), and heroin was identified in 28.1% of the calls. The largest increase occurred in the cases identifying heroin. Heroin-specific calls rose from 62 calls in 2005 to 118 in 2006 – nearly doubling in 1 year. The group identifying methadone exposure showed the smallest increase (+50%; Table 1). Overall, all heroin-related calls increased by 63.6% between 2005 and 2006.

Table 2 summarizes descriptive information about the heroin-related exposure calls. The largest proportion of heroin-related exposures involved males (52.8%; N = 827). Only five of the calls involved heroin-related exposures in pregnant women. The most frequent reported cause of exposure was intentional misuse/abuse (34.1%) followed by unintentional general exposure (27.0%) and suspected suicide (14.4%). Nearly all the exposures reportedly occurred in a personal residence (91.4%). Almost one out of every five exposed persons were under the age of 20, of which 179 were young children aged 0–9 years. However, only three cases of children under the age of 15 years reportedly involved heroin-related exposures; 65 of the children under the age of 15 years were exposed to methadone, and 128 to other/unknown opioids. Out of the 1,565 heroin-related exposures, 884 (56.5%) persons were treated at a health-care facility: N = 242, treated and released; N = 471, treated in a critical care unit; N = 152, treated in a noncritical care unit; and N = 19, treated in a psychiatric care facility. In addition, there were eight recorded fatalities.

The time series of heroin-related calls was characterized by a gradual change in time with no observable step function or pulse function (Fig. 1). In the retrospective analysis, only one statistically significant temporal cluster was identified. In the analysis of heroin-related cases (including methadone and other opioids), both retrospective statistical approaches (scan statistic and Chow test) identified a significant rise in the number of cases in January 2006. Within the retrospective analysis based on reported heroin cases only, the temporal shift identified by the two methods occurred in March 2006.

Table 3 summarizes data on timeliness, critical values, and number of false positives identified by the different prospective statistical approaches. For heroin-related cases, both the ARIMA and the PULSAR methods identified the change in March of 2006 – 2 months after the actual shift began – as detected retrospectively. However, the ARIMA model did not identify any other significant temporal clusters (i.e., "false positives") prior to the January 2006 shift (Table 3). In the prospective analysis based on the smaller subset of reported heroin cases only, the shift was identified in May for all the three methods. The critical values defined by the ARIMA model at α = 0.05 varied between 31.3 for all heroin-related cases and 16.1 for reported heroin cases only. The critical value is the threshold number of cases occurring within any given month that if exceeded represents a significant change.

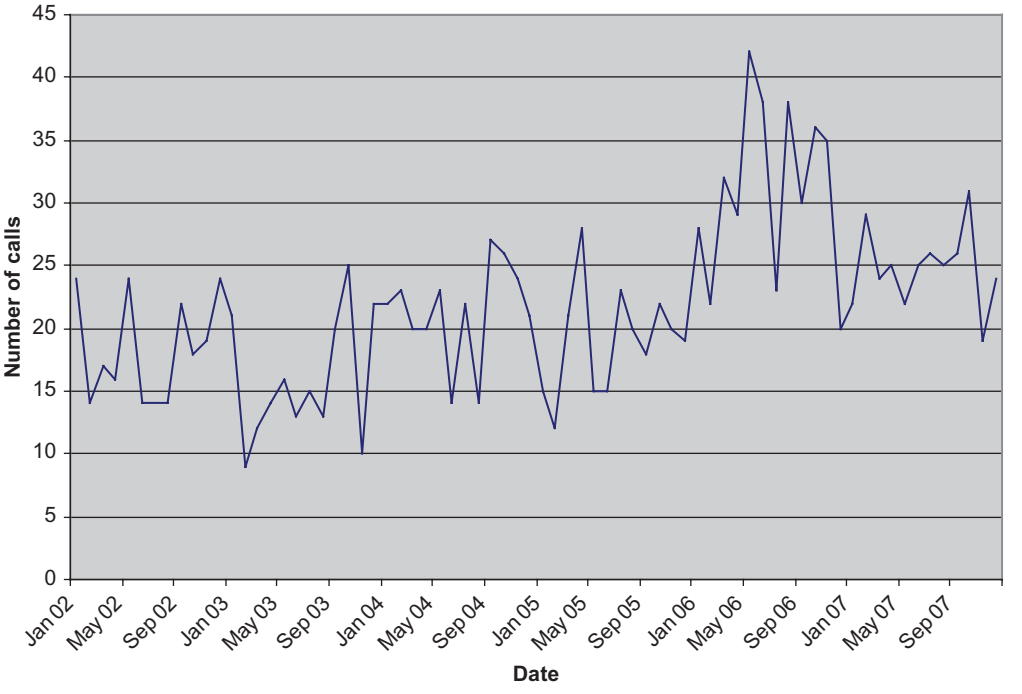

Fig. 1. Frequency of heroin-related calls per month, 2002–2007.

Table 1. Trend in heroin-related calls to the IPC, 2002–2007

Exposure	2002	2003	2004	2005	2006	2007	Total
Heroin	66	48	78	62	118	67	439
Methadone	60	57	71	56	84	85	413
Other/unknown opioids	94	85	107	110	171	146	713
Total	220	190	256	228	373	298	1,565

Table 2. Demographic characteristics of heroin-related calls to the IPC, 2002–2007

	Heroin-related calls (N = 1,565)	Heroin only calls (N = 439)
Gender		
Male	827 (52.8%)	293 (66.7%)
Female	684 (43.7%)	131 (29.8%)
Unknown	49 (3.1%)	13 (3.0%)
Pregnant	5 (0.3%)	2 (0.5%)
Cause of exposure		
Unintentional general	422 (27.0%)	98 (22.3%)
Therapeutic error	161 (10.3%)	0 (0%)
Suspected suicide	225 (14.4%)	27 (6.2%)
Intentional misuse	138 (8.8%)	67 (15.3%)
Intentional abuse	396 (25.3%)	208 (47.4%)
Intentional unknown	38 (2.4%)	5 (1.1%)
Adverse reaction – drug	65 (4.2%)	1 (0.2%)
Adverse reaction – withdrawal	36 (2.3%)	11 (2.5%)
Other	84 (5.4%)	22 (5.0%)
Location of exposure		
Personal residence	1,431 (91.4%)	386 (87.9%)
Public area	35 (2.2%)	26 (5.9%)
Other	99 (6.3%)	27 (6.2%)
Age		
0–9 years	179 (11.4%)	2 (0.5%)
10–19 years	128 (8.2%)	45 (10.3%)
20–29 years	348 (22.2%)	149 (33.9%)
30–39 years	265 (16.9%)	101 (23.0%)
40–49 years	269 (17.2%)	63 (14.4%)
50–59 years	125 (8.0%)	21 (4.8%)
60+ years	76 (4.9%)	3 (0.7%)
Unknown	175 (11.2%)	55 (12.5%)
State		
Illinois	1,532 (97.9%)	435 (99.1%)
Ohio	13 (0.8%)	2 (0.5%)
Other	20 (1.3%)	2 (0.5%)

Discussion

The findings demonstrate that poison center data can be effectively used to actively monitor heroin-related exposures. If there had been a real-time surveillance program using poison center data, the outbreak would have been identified 1 month before the initial reports to the Centers for Disease Control and Prevention (CDC) Epi-X system at the end of April 2006. Although a broad definition for exposure (three drug categories) was used, which likely resulted in the misclassification of cases, poison center data were still able to identify the outbreak earlier than the postmortem data reported to the CDC.[5] A variety of statistical methods were shown to be effective in identifying the outbreak. For this time series, the prospective method that performed best was ARIMA.

Table 3. Prospective analysis of heroin-related calls to the IPC, 2002–2007

	Earliest date identified	Critical value	False positives
Suspected heroin cases[a]			
CUSUM ($\alpha = 0.05$)	May 2006	Na	0
PULSAR ($\alpha = 0.01$)	March 2006	Na	3
ARIMA (0,1,1; $\alpha = 0.05$	March 2006	31.3	0
Heroin cases only[b]			
CUSUM ($\alpha = 0.05$)	May 2006	Na	0
PULSAR ($\alpha = 0.01$)	May 2006	Na	3
ARIMA (0,1,1; $\alpha = 0.05$)	May 2006	16.11	0

[a]Suspected heroin cases include reported exposures to heroin (Poisindex#37702), methadone (Poisindex#37703), or "other/unknown opioids" (Poisindex#37708).
[b]Heroin cases only include reported exposures to heroin (Poisindex#37702).

Although a real-time prospective analysis would not have identified a significant shift in heroin-related calls until March, the retrospective analysis indicates that the outbreak began as early as January 2006 in Illinois. The CDC report based on fatalities indicates that the outbreak began in April.[5] However, the CDC data included deaths from six regions, which may have obscured the findings from Illinois where the drug mixture may have been sold on the streets earlier.

Furthermore, the poison center data indicated that the end of the outbreak in heroin-related poisonings occurred in December 2006, which coincides with the fatality data reported by the CDC.[5] The U.S. Drug Enforcement Administration (DEA) in collaboration with Mexican authorities raided a facility in Toluca, Mexico, in May 2006.[28] This facility was believed to be the source of fentanyl that resulted in the overdoses in the United States beginning in 2006. The highest number of heroin-related calls occurred in May 2006 and was subsequently followed by a decline over the following months (Fig. 1). Calls concerning heroin poisoning, excluding calls for methadone and unspecified opioids,

returned to the pre-2006 levels in 2007. In 2007, the DEA began to regulate the sale and purchase of *N*-phenethyl-4-piperidone, which is used to manufacture fentanyl.[28] Actions by law enforcement in addition to increased prevention activities by public health departments may have contributed to the observed decline in heroin-related overdoses.

Although the poison center data were not based on confirmed exposures to illicit fentanyl, as the exposed person would likely not have known the exact contents of the tainted heroin at the time of the call, it was unlikely that the increase in heroin-related calls and the known overdose outbreak were unrelated. First, we know from confirmed autopsy reports from several major U.S. metropolitan areas that there was a significant and substantial increase in heroin overdoses during the time identified in this study.[5] The medical examiners did provide autopsy confirmation of the presence of fentanyl in the victims.[5] Second, the DEA confirmed that a major crime syndicate from Mexico was mixing fentanyl with heroin.[2] Third, when the DEA and Mexican federal police raided and shut down the suspected factory that was producing the fentanyl, the number of overdoses reported by coroners and the IPC declined. The poison center data do not contradict the known historical facts but substantiate them. If we use Bradford Hill's guide for establishing causation, in this case we have a definitive temporal relationship, the poison center data are consistent with other known sources, the relationship between drug use (+fentanyl) and overdose is highly plausible, there were no reported alternative explanations (e.g., reported increase in heroin concentration, changes in user habits, and influx of new users), the outcome is highly specific (i.e., you would expect an increase in overdoses when fentanyl is mixed with heroin), and the findings were coherent with known outcomes from the use of tainted heroin by street users (e.g., reports from California in the 1980s).[10,11]

The use of broad case definitions is the main method used today in a variety of real-time surveillance programs, in particular syndromic surveillance. For example, an infectious disease rubric in syndromic surveillance may contain up to 200 signs and symptoms. As a general rule, the broader the case definition, the lower the specificity that leads to false alerts. In syndromic surveillance, the primary limiting factor is that confirmation of a toxin often takes several days or weeks; therefore, the use of syndromes based on symptoms or drug prescriptions makes sense in order to reduce the time to detection. The limiting factor when using poison center data is the small sample sizes, particularly when analyzing the data on a daily basis. In addition, if misclassification is a strong possibility, then broad case definitions are an appropriate approach. When dealing with illicit drug use, it is very feasible that callers would misrepresent their exposures and then be misclassified.

The concept of real-time surveillance is to not be correct 100% of the time but to have a system in place that can identify major events as early as possible even if it means identifying a few false alerts in the process.[29] It is unlikely that any real-time surveillance system can reach 100% specificity (i.e., no false positives), but it does not preclude the use of broad case definition categories for this type of surveillance. After all, the interest of real-time surveillance of this nature is to analyze the trend across time rather than a description of the magnitude and nature of an outbreak. Only by analyzing the trend, can a deviation from the norm be identified. An integral part to an effective real-time surveillance system is the response by public health officials to an alert. It is the responders who confirm the alert using multiple data sources and public resources.

The poison center data only picked up eight fatalities compared to the 349 reported to CDC by the Cook County medical examiner.[5] Poison center data are not adequate for capturing fatalities. Furthermore, the gap in observed fatalities may also indicate that poison centers receive calls for only a small fraction of total heroin-related poisonings. Despite likely underreporting, the poison center data still detected the outbreak. Poison center data provide an earlier warning system than postmortem data sources although this data does not adequately quantify the magnitude of an outbreak. This illustrates the need for multiple data sources for real-time surveillance programs, in particular hospital discharge and medical examiner databases.

Poison center data are continuously uploaded by poison centers to a central repository called the National Poison Data System. Many poison centers upload data every couple of minutes. The capture of data is in near real time. The current system is nearing development of allowing users to set thresholds for specific exposures to alert stakeholders when an exposure exceeds a certain number of cases during a specific unit of time. If a number of events in a given window of time exceed the threshold value, the appropriate personnel in the poison center or other public health agencies would be automatically notified. This should be a major priority of the American Association of Poison Control Centers for the National Poison Data System.

Conclusion

The most recent fentanyl outbreak illustrated the need for identifying and establishing effective and responsive real-time surveillance tools to monitor drug overdoses in the United States.[5] This study showed that poison center data would have identified the outbreak 1 month before the initial reports to the CDC. Fentanyl exposures through street drug use are a recurring public health problem[11–14] as are many other types of poisonings. Poison center data are national in scope and may be effectively used for real-time surveillance of a variety of toxic exposures that range from carbon monoxide poisoning to illicit drug use. Threshold values derived from prospective analyses can be estimated for a wide range of exposures to improve real-time public health surveillance.

Declaration of interest: The author is a consultant to the Illinois Poison Center for their Latino outreach and health

educator programs. This project is funded through a grant from the Illinois Department of Public Health and the Illinois Poison Center. The author alone is responsible for the content and writing of the article.

Acknowledgments

Thanks to Dr. Michael Wahl of the IPC and Dr. Daniel Hryhorczuk of the University of Illinois at Chicago School of Public Health for assisting in acquiring the data and funding for this project. Thanks to Dr. Linda Forst for providing her feedback on the final draft of this manuscript.

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