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Syndromic Surveillance using Poison Center Data: An Examination of Novel Approaches

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ABSTRACT

SYNDROMIC SURVEILLANCE USING POISON CENTER DATA: AN EXAMINATION OF NOVEL APPROACHES

By

KAI YEE LAW

JULY 22, 2016

Surveillance is a key component of public health practice. Early detection of a new outbreak or new information about a public health issue could prevent morbidity and mortality and reduce healthcare expenditures for the economy. Syndromic surveillance is a subset of public health surveillance practice that uses pre-diagnostic data to monitor public health threats. The syndromic surveillance approach posits that patients first interface with the healthcare system in non-traditional ways (e.g., buying over-the-counter medications, calling healthcare hotlines) before seeking traditional healthcare avenues such as emergency rooms and outpatient clinics. Thus detection of public health issues may be more timely using syndromic surveillance data sources compared to diagnosis-based surveillance systems.

One source of information not yet fully integrated in syndromic surveillance is calls to poison centers. United States poison centers offer free, confidential medical advice 24 hours a day, seven days a week through a national help line to assist in poison exposures. Call data are transmitted and stored in an electronic database within minutes to the National Poison Data System (NPDS), which can be used for near-real-time surveillance for disease conditions or exposures.

The studies presented in the dissertation explore new ways for poison center records to be used for early identification of public health threats and for evaluating policy and program impact by identifying changing trends in poison center records. The goals of the studies were 1) to assess whether poison center records can be used for surveillance of noninfectious foodborne disease outbreaks (FBDOs) and assess whether certain features of poison center records are more likely associated with a confirmed noninfectious FBDO, 2) to assess whether state public health interventions such as prescription drug monitoring programs were associated with a reduction in opioid use trends, and 3) to assess whether state legislation such as recreational marijuana legalization was associated with an increase in marijuana and reduction in synthetic cannabinoid use trends.

The approach and findings from these three studies expand upon current knowledge of how poison center records can be used for syndromic surveillance and provide evidence that justifies expansion of poison center surveillance into avenues not yet explored by local, state, and federal public health.

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by

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APPROVAL PAGE

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Author's Statement Page

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Chapter 1: Introduction to Syndromic Surveillance and Poison Center Data

1.1 Background

Surveillance is a key component of public health practice. Constant and accurate monitoring for current and emerging public health threats is one of the most important missions in public health (Lee, Thacker, Teutsch, & Louis, 2010). Early detection of a new outbreak or new information about a known public health issue could prevent morbidity and mortality and reduce healthcare expenditures for the economy. The field of public health surveillance grew from basic mortality monitoring in the 17th century, and today includes a range of different data sources to monitor a multitude of diseases and conditions (Eylenbosch & Noah, 1988).

Syndromic surveillance is a subset of public health surveillance practice that uses pre-diagnostic data to monitor public health threats. The syndromic surveillance approach posits that patients first interface with the healthcare system in non-traditional ways such as buying over-the-counter (OTC) medications or calling healthcare hotlines before seeking healthcare in ways identifiable in traditional public health surveillance systems (Chen, Zeng, & Yan, 2010). While syndromic surveillance lacks case confirmation accuracy compared to its lab-based or diagnostic-based surveillance counterparts, this emerging field may be able to identify threats quicker for more prompt public health response. One source of information not yet fully integrated in syndromic surveillance approaches is calls to poison centers. United States poison centers offer free, confidential medical advice 24 hours a day, seven days a week through a national help line to assist in poison exposures. Call data are transmitted and stored in an electronic database every eight minutes to the National Poison Data System (NPDS), which can

be used for near-real-time surveillance for disease conditions or exposures and to provide situational awareness during incidents of public health significance (Wolkin, Martin, Law, & Schier, 2011). The purpose of this dissertation is to examine the ability for poison center calls to identify and monitor current and emerging public health threats using syndromic surveillance analytical approaches.

1.2 Public health surveillance definition

Public health surveillance is the ongoing and systematic collection, management, analysis, and interpretation of data followed by the dissemination of these data to public health programs to stimulate public health action (CDC, 2012). The modern concepts of public health surveillance were derived from public health activities developed in the past to control disease spread in a community. In the 1680's, analysis of mortality was used in health planning in London (Eylenbosch & Noah, 1988). In the United States, basic elements of public health surveillance were found in Rhode Island in 1741, where colonies passed laws requiring the reporting by taverns of contagious diseases (Thacker, Qualters, & Lee, 2012). While historically public health surveillance used mortality data and tracked infectious diseases, the field has since broadened to include a variety of data sources for all aspects of public health activities (Lee, Thacker, Teutsch, & Louis, 2010). Regardless of the broadening of surveillance in public health, the definition of public health surveillance remains unchanged after more than thirty years, given its flexibility and applicability even in the modern days of surveillance practice. The practice of public health surveillance today is much more complicated and continually changing with advancements in technology and analytic methods.

Traditional public health surveillance systems rely on physicians' reporting and laboratory testing of diseases and conditions important for public health. These activities are considered the backbone of surveillance activities; one of the main indicators of a nation's disease surveillance capability is based on its laboratory testing capabilities (Hamburg, Sparling, Choffnes, & Mack, 2007). Traditional surveillance systems include voluntary physician reporting and laboratory testing from sentinel sites such as emergency room departments and physician offices, and the reported diseases can cover a wide range of conditions based on the needs of the public health jurisdiction. Examples of traditional surveillance systems that use physician reporting or laboratory testing include the National Notifiable Disease Surveillance System, the National Respiratory and Enteric Virus Surveillance System and the Foodborne Diseases Active Surveillance Network, all United States (US) national surveillance systems which have the highest confirmatory accuracy compared to other types of surveillance systems but may take weeks to a month for reporting (NREVSS, 2015; FoodNet, 2015; NNDSS, 2015). Traditional surveillance systems can also focus on subsets of more severe inpatient illnesses, including those involving intensive care unit (ICU) support and death (NVSS, 2015). All of these types of surveillance systems listed above monitor disease trends among inpatient populations and can only capture those that seek care at a healthcare facility (Fricker, 2013).

The traditional physician-laboratory surveillance network has its strengths and weaknesses. Given data sources such as physician diagnoses and laboratory results which have higher confirmatory accuracy, the data are more specific than those using pre-diagnostic data. Also, the availability of identifiable information for each case makes it possible to initiate epidemiological investigation and intervention early (Koutsonanos, 2014). On the other hand,

the time and cost required for case confirmation through laboratory confirmation or physician reporting can substantially delay an effective public health response.

1.3 Syndromic surveillance definition

The term syndromic surveillance originally referred to the gathering of information about patients' symptoms (such as coughing or fever) during the early phases of illness (Hennig, 2003). Although syndromic surveillance was developed for early detection of large-scale releases of biologic or chemical agents, the current goals and uses of syndromic surveillance span across all aspects of public health (Hennig, 2004). There are two generally accepted definitions of syndromic surveillance used in the literature: 1) to conduct public health surveillance using health-related data that precede diagnosis and signal a sufficient probability of a case of an outbreak to warrant further public health response (Syndromic Surveillance, 2015; Mandl, et al., 2004; Palvin, 2003); 2)and an investigational approach assisted by automated data acquisition and generation of statistical alerts to monitor disease indicators in real-time or near real-time to detect outbreaks of disease earlier than would otherwise be possible with traditional public health methods (Hennig, 2004; Buehler, Hopkins, Overhage, Sosin, & Tong, 2004). Thus, syndromic surveillance is public health surveillance restricted to leading indicators of disease (Fricker, 2013). Of particular distinction of syndromic surveillance to other surveillance approaches, particularly traditional surveillance systems, is the use of pre-diagnostic data to detect trends and outbreaks. Certain syndromic surveillance programs monitor surrogate data sources such as OTC medication sales or school absenteeism data that may be indicative of an emerging public health threat (Debjani, Metzger, & Hefferman, 2005; Rodriguez, Zhang, & Leguen, 2007). Other programs monitor groups of signs and symptoms

(syndromes) potentially indicative of a public health threat (e.g., gastrointestinal symptoms for a norovirus outbreak) using pre-diagnostic clinical data such as chief complaints reported to the emergency department (Hefferman & Mostashari, 2004). Data sources for syndromic surveillance mostly fall into two general categories: 1) the use of health care services such as patient visits to clinics or emergency departments (ED), ambulance dispatch records, health hotline calls, laboratory test requests; and 2) indicators of health-related behaviors, such as the purchase of OTC medicines or absence from school or work (Mandl, et al., 2004; Koutsonanos, 2014). A list of common syndromic surveillance data sources are listed in Table 1-1.

Table 2-1. Clinical-based and alternative data sources commonly used for syndromic surveillance **(Hennig, 2004)**.

Clinical-based data sources
Emergency department (ED) patient volume
Total admissions from ED
ED triage log of chief complaints
Ambulatory-care clinic outcome
Emergency medical system (911) call type
Provider hotline volume, chief complaint
Poison center calls
Insurance claims or billing data
Clinical laboratory or radiology order volume
Alternative data sources
School absenteeism
Work absenteeism
Over-the-counter medication sales
Volume of internet-based health inquiries
Internet-based illness reporting
Animal illnesses or deaths

The primary objective of syndromic surveillance is to identify trends or clusters early and before diagnoses or laboratory tests are confirmed for timely public health response to reduce morbidity and mortality. The classic depiction of the potential advantages to syndromic surveillance is shown in Figure 1-1. The figure shows epidemic curves for individuals from symptom onset to severe illness for a hypothetical outbreak. The time between identification of

increases in symptom onset for the population and the subsequent patient visits to a health-care facility to obtain a laboratory test or physician diagnosis is denoted by t. The aim of syndromic surveillance is to identify the increases in symptom onset t days earlier than identification of increases in confirmed cases, allowing public health to respond t days earlier than just using traditional public health surveillance. The size of t depends on many factors, including the type and size of the outbreak, data source, analysis approach, and case threshold determination.

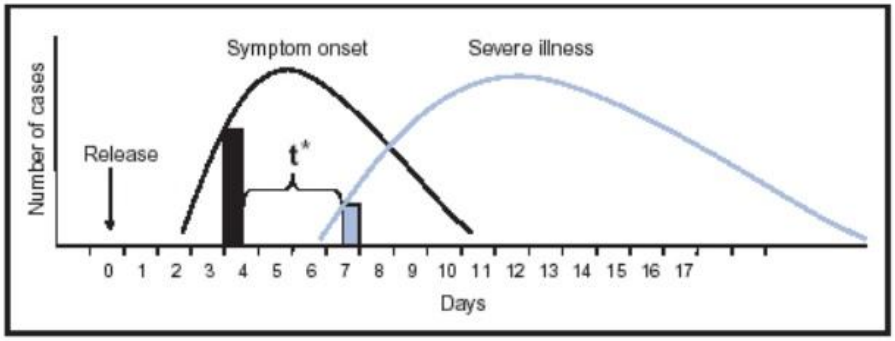

Figure 1-1. Identification of symptom onset may detect adverse events earlier than identification of increases in severe illness **(Hennig, 2004)**.

There are several key features of syndromic surveillance systems. As pre-diagnostic indicators of illness, data sources are usually only approximations of disease status, such as chief complaint, laboratory test requests, absenteeism, and poison center calls (Koutsonanos, 2014). Data acquisition and analysis is automated or partially automated, and in real-time or near-real time (Lawson & Kleinman, 2005). Aberrant trends in the indicator data are identified via computerized tools. Syndromic surveillance is considered to be superior to traditional surveillance in timeliness and sensitivity (Buehler, Hopkins, Overhage, Sosin, & Tong, 2004; Provincial Infectious Diseases Advisory Committee, 2012). However, some authors have

questioned the current trend of dramatically increased investment and implementation of syndromic surveillance, without clear system capabilities and assessment for system validity, especially considering information sources are opportunistic datasets (Lee, Thacker, Teutsch, & Louis, 2010; Chen, Zeng, & Yan, 2010). Nonetheless with the advent of 'big data' and rapid growth in information technology, syndromic surveillance has moved very quickly from theory to public health practice.

Examples of prominent syndromic surveillance systems include the Electronic Surveillance System for the Early Notification of Community-based Epidemics (ESSENCE). ESSENCE is considered one of the oldest and most mature syndromic surveillance systems built in collaboration between the Johns Hopkins University Applied Physics Laboratory and the Walter Reed Army Institute of Research. The system monitors both military and civilian healthcare data daily for early outbreak detection and warning, fusing information from multiple data sources that vary in medical specificity and time-scale behavior (Lombardo & Burkom, 2004; Burkom & Elbert, 2004). Its main source of data is emergency department chief compliant data from participating military and civilian medical facilities and the system allows for automated aberration detection of outbreaks and web-based visualization of data (Chen, Zeng, & Yan, 2010). The system has since been adapted by many state and local public health jurisdictions (Florida Surveillance Systems , 2015; Oregon ESSENCE, 2015). Some of these adaptations allow the inclusion of other syndromic data sources; Florida's ESSENCE system incorporates chief complaint data and call data from Florida poison centers as a part of its syndromic surveillance system (Florida Surveillance Systems , 2015).

1.4 Poison center data, operations, and repository

The US has 55 poison centers available free of charge to users 24-hours a day, every day of the year, through a national telephone hotline 1-800-222-1222 (American Association of Poison Control Centers , 2015). Callers are routed to the appropriate poison center-based on the location of the call. These call centers respond to questions from the public and health care professionals. The poison centers serve the entire population of the 50 states, American Samoa, District of Columbia, Federated States of Micronesia, Guam, Puerto Rico, and the US Virgin Islands (American Association of Poison Control Centers , 2015). Encounters with callers involve either an exposed human or animal (exposure call) or a request for information with no person or animal exposed to any substance (information call). During 2013, US poison centers received more than 3 million exposure and information calls (Mowry, Spyker, Cantilena, McMillan, & Ford, 2014). Exposures reported by callers to poison centers span the entirety of toxicological exposures, including accidental pediatric ingestions, pharmaceutical overdoses, industrial accidents, snake bites, and contaminated food incidents (Mowry, Spyker, Cantilena, McMillan, & Ford, 2014).

Calls are managed by health care professionals who have received specialized training in clinical toxicology. These providers generally include medical and clinical toxicologists, registered nurses, doctors of pharmacy, and pharmacists, and are referred to as specialists in poison information (SPIs) (American Association of Poison Control Centers , 2015). They direct the public to the most appropriate level of care and provide the most up-to-date management recommendations to health care providers caring for exposed patients. Medical toxicologists are available on-call to respond for calls from healthcare professionals requesting toxicological

consult on a patient. Poison centers undergo an accreditation process administered by the American Association of Poison Control Centers (AAPCC) and must be reaccredited every 5 years (Guyer & Mavor, 2005).

Data fields from each call are logged in a separate record and stored in local poison center servers. SPIs record data from each call using a data entry system. Each data entry platform produces call records in a standard format with fields standardized by the American Association of Poison Control Centers. Case records undergo variable, poison center-specific auditing procedures to ensure appropriate call data management and data capture. Data variables collected reflect the primary function of triage and patient management for poison centers, which include basic call information (exposure call vs. information call), demographic information (age, gender of the exposed individual), caller contact information (name, address, phone number, affiliation), scenario information (caller site), exposure information (substance, chronicity, clinical effects, duration, site), treatment information (therapy or therapies recommended), and medical outcome (American Association of Poison Control Centers , 2015). The data entry platforms also provide the SPIs with free-text fields for case notes to transcribe the details given by the caller.

Exposure substances are categorized by a proprietary product database maintained and continuously updated by the Micromedex Poisindex System, a subsidiary of Truven Health Analytics (Micromedex , 2015). The database contains more than 400,000 products, ranging from viral and bacterial agents to commercial and drug products. A generic coding system categorizes the database into 1,081 generic codes. These codes are classified under 122 major

pharmaceutical categories and 36 major non-pharmaceutical categories, and further classified into subcategories (American Association of Poison Control Centers , 2015).

A de-identified subset of the information fields entered by the SPI in the data collection platforms are uploaded to a national data repository and surveillance system called the National Poison Data System (NPDS) on average every 8 minutes (National Chemical and Radiological Surveillance Program , 2015; American Association of Poison Control Centers , 2015). The uploaded fields include the fields relevant to public health, but omit information identifying the patient or caller (name, address). Free-text case notes are not uploaded to protect caller privacy concerns and because of system limitations.

The National Poison Data System (NPDS) is a web-based data repository and surveillance system consisting of selected data fields of all call records from all US poison centers. Nationally, NPDS has been used as an active surveillance system (i.e., collection of clinical information through healthcare professional case reporting) and a passive surveillance system (i.e., no specific case-reporting for data collection). NPDS has more than 60 million records on call records dating back to 2000 (American Association of Poison Control Centers , 2015) (National Chemical and Radiological Surveillance Program , 2015). Data within NPDS are owned by AAPCC and all use and access to NPDS data are subject to approval by AAPCC.

The enterprise reporting function of NPDS allows users to query data dating back to 2000 based on any user-defined parameters. Visualization functions can show queries temporally and spatially. The wide array of enterprise reporting options provide immense flexibility in reporting and visualization that generates results within seconds to minutes. Reports can be exported to a variety of formats for importation into other software programs for more complex statistical analysis.

1.5 Current use of poison center data for public health surveillance

Poison center data have been used for a variety of public health surveillance purposes at the local, state, federal, and international levels (Spiller & Griffith, 2009). Poison center data have been used to detect threats or monitor emergence of trends in: 1) cases of drug and substance abuse (Law, Schier, Martin, Chang, & Wolkin, 2015; Kasper & Ridpath, 2015; Hughes, Bodgan, & Dart, 2007; Rosenson, Smollin, Sporer, Blanc, & Olson, 2007; Dart, Surratt, & Cicero, 2015), 2) foodborne illness outbreaks (Derby, McNally, & Ranger-Moore, 2005; Wolkin, Martin, Law, & Schier, 2011; Gruber, Bailey, & Kowalcyk, 2015), 3) product and medication contamination (Wolkin, Martin, Law, & Schier, 2011; Gryzlak, R, Zimmerman, & Nisly, 2007), and 4) injuries from commercial and consumer products (Chatham-Stephens, Law, & Taylor, 2014; Pillai, Law, Beuhler, & Henretig, 2012). Additionally, poison center data have been used to monitor selected illnesses in the general population (e.g., influenza), and for situational awareness following known man-made or natural disasters (Simone & Spiller, 2010; Kay, Blackmore, & Schauben, 2006; Clower, Henretig, & Trella, 2012).

At the federal level, routine surveillance activities are conducted using NPDS. The web-based NPDS software offers many surveillance functionalities allowing approved public health agencies (e.g., state health departments, CDC) to use NPDS data. Users also can create custom surveillance definitions to prospectively monitor NPDS data using a variety of parameters (Wolkin, Martin, Law, & Schier, 2011; National Chemical and Radiological Surveillance Program , 2015). Surveillance activities have been used to identify gas and vapor incidents (e.g., methane releases, carbon monoxide incidents) and food-related incidents (Law, Sheikh, & Bronstein, 2014).

1.6 Gaps in syndromic surveillance using poison center data

The immediacy of data availability and pre-diagnostic nature of poison center calls lends this dataset well to syndromic surveillance. The data can be uploaded and analyzed in a timely manner and the product coding of reported exposures allows for high specificity of the implicated substance of exposure. Moreover, the broad range of calls received by poison centers allows for surveillance of many exposure categories as evidenced by the description of poison center data uses mentioned above. Despite these opportunities, poison center data are not yet fully integrated into public health surveillance practice in the US; recent surveys reveal 52% of state health departments have real time or near real time data access to local poison center data, compared to over 80% for emergency department chief complaint data (Kintziger, Miller, Simms, Stanbury, & Watkins, 2012; Assessment Report on the Collaboration between Health Departments and Poison Centers, 2015; Chen, Zeng, & Yan, 2010). One contributing factor to suboptimal uptake of poison center data for state syndromic surveillance systems is that a percentage of public health departments do not yet know how poison center data can supplement current state surveillance activities (Assessment Report on the Collaboration between Health Departments and Poison Centers, 2015). Better justifications and examples of how poison center data can be integrated into public health practice particularly syndromic surveillance, perhaps through the ability for poison center data to detect events and trends earlier than traditional public health surveillance, can push poison center data further into the realm of syndromic surveillance and public health practice.

Moreover, syndromic surveillance sources such as poison center data are typically analyzed using traditional aberration detection methods. Techniques include statistical process

control such as the historical limits method and change point analyses (Fricker, 2013). The sensitivity, specificity, and timeliness of detection for different techniques vary significantly and depend widely upon the desired target of the researcher. Consequently, many of these techniques are only effective for detecting sudden major changes in time series data and have limited ability to identify subtle and potentially important changes in time series trends. The studies described below examine using novel approaches for earlier detection of public health threats and changes in trends.

1.7 Studies

This dissertation will focus on novel approaches to using poison center data for identification of emerging public health threats and changes in trends. The first study will add to the understanding of how poison center data can be best incorporated into syndromic surveillance through comparisons with 'gold standard' traditional public health surveillance systems. The second and third studies push the traditional paradigm of using syndromic surveillance data for aberration detection into more sophisticated time-series designs for the purpose of early detection of subtle trends following public health interventions and state legislation.

Study #1 - Using poison center data for noninfectious foodborne illness surveillance

Foodborne disease is a pervasive problem caused by consumption of contaminated food or drink. An estimated 48 million foodborne illnesses occur annually in the United States (US), resulting in over 128,000 hospitalizations and 3,000 deaths (CDC, 2016). A foodborne disease outbreak (FBDO) is defined as an incident in which two or more persons experience a similar

illness resulting from the ingestion of a common food (CDC, 2000). While a majority of FBDOs can be traced to an infectious source, noninfectious agents can also contaminate food products and cause adverse health effects including severe illness and death (CDC, 2013). The Centers for Disease Control and Prevention tracks investigations of noninfectious FBDOs in the US through the Foodborne Disease Outbreak Surveillance System (FDOSS) (CDC, 2013). FDOSS constitutes the most comprehensive repository of confirmed noninfectious FBDOs in the US but data collection lacks timeliness. A supplemental and timely data source for noninfectious FBDO surveillance is warranted to reduce morbidity and mortality from noninfectious FBDOs and reduce noninfectious FBDO events.

The first objective of this study was to assess whether poison center records can be used for surveillance of noninfectious FBDOs. I assessed feasibility by determining whether confirmed outbreaks captured in FDOSS were also captured in a timelier manner by poison center records. The second objective was to assess whether certain features of poison center records were more likely associated with a confirmed noninfectious FBDO reported to FDOSS. I matched poison center records to outbreaks reported in FDOSS by etiology, state, and call date or date of first reported illness (±7 days) to identify events reported to FDOSS captured by NPDS. We used multiple logistic regression on poison center records to assess the relationship between a poison center record that matched a confirmed noninfectious FBDO and healthcare facility caller and case severity.

Among noninfectious FBDOs reported to FDOSS, 31% (188 of 614) of outbreaks were matched to 5% (468 of 8,773) poison center records by matching criteria. These findings suggest that NPDS does capture a significant percentage of noninfectious foodborne outbreak

events and illnesses. Given the timeliness and availability of data capture, NPDS data can be used as a timely supplemental surveillance system for noninfectious foodborne outbreaks. The multivariable logistic regression model selection indicated statistically significant predictors of concordance of NPDS and FDOSS: severity, healthcare facility caller, etiology, and age. The findings from the logistic regression model predictors suggest there are particular features of NPDS records that may be more indicative of a confirmed noninfectious FBDO.

Study #2 – Effect of prescription drug monitoring program implementation on opioid- and heroin-associated exposures called to poison centers

Prescription opioid abuse is the intentional, non-medical use of an opioid to obtain a euphoric or psychotropic effect. Abuse of prescription opioids is a substantial public health problem in the United States (US); an estimated 1.9 million people suffered from substance abuse related to prescription opioids in 2013 an estimated sixteen thousand people died in the US due to prescription opioid medications in 2010 (Dart, Surratt, & Cicero, 2015; SAMHSA, 2014). One type of intervention cited as having significant potential in reducing opioid abuse and misuse is prescription drug monitoring programs (PDMPs). PDMPs are statewide electronic databases that collect prescription data from prescribers and dispensers on medications classified as federal controlled substances. PDMPs are designed to assist in detecting and preventing abuse, misuse, and diversion of controlled substances by reducing the incidence of 'doctor shopping'. This occurs when patients see multiple providers and pharmacies with the intent of obtaining controlled substances for misuse. States have yet to publish the effectiveness of PDMPs on opioid-related illnesses and deaths resulting from abuse. Moreover, no studies have examined the relationship between prescription opioid abuse and heroin use at

the state level. The objective of this study was to use poison center records to assess whether PDMP implementation is associated with a reduction in the time trend of opioid-associated calls and an increase in the time trend of heroin-associated calls. We conducted a time series analysis of opioid and heroin use and abuse captured by poison center records, defined in this study as the ratio of monthly opioid- or heroin-associated calls to non-steroidal anti-inflammatory drug-associated (NSAID) calls within the state. Two states were chosen as a part of this analysis; the first state implemented a state-wide PDMP in the winter of 2011 and is the intervention state in this study. A second state was chosen (the control state) which implemented a PDMP after November 2013 outside the study period.

The findings of the study included the intervention state significantly attenuated the expected trend of rising opioid trends following implementation of the PDMP. The effect was immediate as evidenced by the ratio decrease in the month following implementation. Moreover, the effect persisted during the rest of the study period as the trend sloped downward in the months following implementation. However, decreased opioid trends following implementation seen in state A were also associated with increases in heroin trends. The intervention state saw an increase in heroin trends following PDMP implementation and this effect persisted during the rest of the study period. The immediate and persistent effects of PDMP implementation on the opioid to NSAID ratios in the intervention state suggested that PDMP implementation does affect opioid abuse rates at the state level. The associated increases in heroin to NSAID ratios following PDMP implementation suggest a substitution effect was present as availability of prescription opioids for abuse declines. The approaches in

this study provided a framework for detecting changing trends in poison center records for assessment of public health interventions such as PDMP implementation.

Study #3 – Effect of state marijuana legislation on marijuana and synthetic cannabinoid use

Marijuana has long been used for its neuropsychiatric effects including enhanced relaxation and perceptual alterations (Green, Kavanagh, & Young, 2003). The primary active ingredient of marijuana is Tetrahydrocannabinol (THC), which binds to the cannabinoid receptors in the body. Synthetic cannabinoids also bind to the same cannabinoid receptors. Synthetic cannabinoids have gained popularity in the past decade as recreational drugs because it is believed use of these substances result in a marijuana-like high.

Currently, marijuana use for any purpose is criminalized at the federal level, although there have been piecewise changes at the state level for decriminalization for medical and recreational marijuana. There are no published state-specific studies on marijuana use following legalization. Alternatively, one of the main drivers of the popularity of synthetic cannabinoids is that they are not detectable in typical urine drug screens for marijuana and THC. Synthetic cannabinoid use, however, is a more harmful alternative to traditional marijuana and its use avoids the legal penalties associated with marijuana use (Bonar, Ashrafioun, & Ilgen, 2014). Thus, one of the potential effects of recreational and medical marijuana legalization is the decrease in synthetic cannabinoid use as those who were using synthetic cannabinoids may switch to a legal, regulated, and less harmful alternative. There have not been any studies examining the effect of marijuana laws on synthetic cannabinoid use.

The objective of this study was to assess whether recreational marijuana legalization was associated with an increase in marijuana-associated calls and reduction in synthetic

cannabinoid-associated calls by using the ratio of synthetic cannabinoid records to marijuana records in NPDS. I applied a longitudinal time series design of synthetic cannabinoid to marijuana ratio trends captured by poison center records. Three states were chosen as a part of this study to reflect the three categorizations of marijuana laws. State A legalized recreational marijuana use for people over 21 years old in December 2012 and is the intervention state in this study. The second state chosen (state B) legalized medical marijuana and the third state chosen (state C) prohibits both medical and recreational marijuana use.

State A saw a decrease in synthetic cannabinoid to marijuana ratio following legalization of recreational marijuana. The effect was immediate as evidenced by the drastic ratio decrease in state A in the month following legalization. Alternatively, states B and C did not see any significant changes in ratio over the same time period. The immediate effects of recreational marijuana legalization on the synthetic cannabinoid to marijuana ratios in state A suggested that relaxing marijuana laws attenuated the substitution of marijuana for synthetic marijuana at the state level. The approaches in this paper provided a framework for detecting changing trends in NPDS records for assessment of state policies such as marijuana legalization.

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Chapter 2: Using Poison Center Data for Noninfectious Foodborne Illness Surveillance

2.1 Introduction

Foodborne disease is a pervasive problem caused by consumption of contaminated food or drink. An estimated 48 million foodborne illnesses occur annually in the United States (US), resulting in over 128,000 hospitalizations and 3,000 deaths (CDC, 2016). Much of these illnesses occur as a result of a foodborne disease outbreak. A foodborne disease outbreak (FBDO) is defined as an incident in which two or more persons experience a similar illness resulting from the ingestion of a common food at a comparable time and place (CDC, 2000). Foods and beverages can be contaminated with infectious agents (e.g., Salmonella, Campylobacter) or noninfectious agents (e.g., Scombroid toxin, heavy metals). While a majority of FBDOs can be traced to an infectious source, noninfectious agents can also contaminate food products and cause adverse health effects including severe illness and death (CDC, 2013). Noninfectious agents implicated in FBDOs include marine toxins (e.g., Ciguatera, paralytic shellfish), mushroom toxins (e.g., muscinol, amanita), heavy metals (e.g., arsenic, mercury), and food additives (e.g., monosodium glutamate).

Surveillance of FBDOs is critical in responding to and preventing foodborne disease illnesses. Investigations during and following surveillance can identify common or rare foods associated with FBDOs. Data from outbreaks provide information on sources of foods where outbreaks occur. This information can help target interventions to reduce foodborne diseases. Data from outbreaks also can help researchers identify changes over time in commonly reported foods and provide insight into the effectiveness of regulations and control measures (CDC, 2013).

Many national foodborne disease surveillance systems such as the Foodborne Diseases Active Surveillance Network (FoodNet) and the Molecular Subtyping Network for Foodborne Disease Surveillance (PulseNet) focus on timely identification of infectious FBDOs through microbial identification and laboratory confirmation of bacterial and parasitic contaminants (CDC, 2013; CDC, 2016). However, these national surveillance systems do not track noninfectious FBDOs. The Centers for Disease Control and Prevention tracks investigations of infectious and noninfectious FBDOs in the US through the Foodborne Disease Outbreak Surveillance System (CDC, 2016). CDC collects reports of FBDOs from state, local, and territorial public health agencies; the Foodborne Disease Outbreak Surveillance System (FDOSS) serves as the repository for investigations initiated by state, local, or territorial public health agencies related to FBDOs.

Approximately 5% of FBDOs in FDOSS are attributed to noninfectious agents (CDC, 2013). Despite this low percentage, noninfectious FBDOs account for a significant amount of food-related illnesses and hospitalizations. Studies estimate ciguatera and scombroid poisonings, which constitute only two of the many noninfectious agents that may be associated with a foodborne outbreak, account for over 50,000 illness (estimated from the number of individuals that seek treatment from a physician) and 500 hospitalizations in the US annually (Pennotti, Scallan, & Backer, 2013).

FDOSS constitutes the most comprehensive repository of confirmed noninfectious FBDOs in the US but data collection lacks timeliness. Confirmation of the outbreak may take days to weeks depending on the resources needed to respond, and reporting from state and local public health departments often occurs in bulk and can take months. As a result,

information collection critical to noninfectious FBDO surveillance such as commonly implicated food sources and outbreak settings is delayed, which delays national public health assessment and response (CDC, 2013). A supplemental data source for timely surveillance of noninfectious FBDOs is warranted to reduce morbidity and mortality from noninfectious FBDOs.

United States poison centers offer free, confidential medical advice 24 hours a day, seven days a week through a national helpline to assist in poison exposures. Poison centers receive calls from both healthcare providers and the public, with 15% of call from healthcare providers and 85% of call from the public (Mowry , Spyker , & Cantilena, 2014). While utilization of poison centers are dependent on demographic characteristics, studies estimate that about seven per thousand population use poison center services annually (Litovitz & Benson, 2010). Reported exposures include noninfectious foodborne exposures. Call data are transmitted and stored in an electronic database every eight minutes to the National Poison Data System (NPDS), which can be used for near-real-time surveillance for disease conditions or exposures and to provide situational awareness during incidents of public health significance (Wolkin, Martin, & Law , 2012). Previous studies have shown that NPDS-based syndromic surveillance may be a useful addition to surveillance data reported to state public health agencies for the early detection of infectious FBDOs, but no studies have assessed using NPDS records for national surveillance of noninfectious FBDOs (Derby, McNally, & Ranger-Moore, 2005). NPDS may be a useful and timely supplemental tool in conducting surveillance of noninfectious FBDOs because of the specificity of the implicated substance of exposure and timeliness of data collection. If the data are reliable, NPDS records may be ideal for timely assessment of time, location, and spread of a noninfectious FBDO. Moreover, timelier collection of FBDO

information for surveillance can reduce intervention delay and reduce the incidence of noninfectious foodborne illnesses in the US. However it remains to be seen whether NPDS captures the same events as those confirmed to be noninfectious FBDOs in FDOSS.

The first objective of this study was to assess whether NPDS records can be used for surveillance of noninfectious FBDOs. I assessed feasibility of using NPDS records for noninfectious FBDO surveillance by determining whether confirmed outbreaks eventually recorded in FDOSS (the gold standard of noninfectious FBDOs) were also captured in a timelier manner by NPDS records. Contaminants implicated in noninfectious FBDOs include marine toxins (ciguatera, scombroid, and shellfish neurotoxin), heavy metals, monosodium glutamate (MSG), and mushroom toxins (Scallan, Griffin, & Angulo , 2010). The second objective was to assess whether certain features of NPDS records were more likely associated with a confirmed noninfectious FBDO reported to FDOSS.

2.2 Methods

Data Sources

FDOSS

State, local, and territorial public health departments identify and investigate outbreaks and voluntarily report outbreaks using a standard, internet-based form to FDOSS. Outbreaks reported to FDOSS are confirmed by public health departments, and therefore are considered a gold standard for tracking noninfectious FBDOs (CDC, 2013). Data collected for each outbreak include the date of first reported illness, location of the outbreak, estimated number of individuals affected, and FBDO etiology. Outbreak reporting depends on the public health department, but generally occurs within one to three months Annual summaries and analyses

of FDOSS reports are used to provide updates on the human health impact of FBDOs (CDC, 2016). We reviewed all outbreaks reported to FDOSS with a noninfectious etiology from 2000–2010. Outbreaks with unknown chemical or toxic etiology were excluded from the analysis due to the inability to find a corresponding NPDS etiology category for matching. Information collected for each outbreak for descriptive analysis and matching included outbreak etiology, date of illness onset, reporting state, and number of individuals affected. Outbreak information in FDOSS included the number of individuals affected, so each outbreak record may be associated with multiple illnesses.

NPDS

Healthcare professionals and the public call poison centers for consultation of poison exposures. A subset of data collected by poison centers is uploaded to NPDS every eight minutes. NPDS captures standardized information on each call received by a poison center including the implicated substance of exposure, patient demographics (age and sex), and clinical and case management data. Each NPDS record is assigned a specific substance code to identify the substance(s) of exposure and enable surveillance. NPDS users can query the data using a combination of substance codes, clinical data, and health outcomes. We queried all NPDS records whose implicated substance matched the list of noninfectious FBDO etiologies in FDOSS data. Substances included scombroid toxins, ciguatera toxins, paralytic shellfish poison (PSP), monosodium glutamate (MSG), amanita, heavy metals (selenium, chromium, and cadmium), methomyl, and tetrodotoxin. Data were queried for 2000–2010. Animal-related exposure records and records confirmed as non-exposures by poison center staff were excluded from the analysis. Information collected by each NPDS record for descriptive analysis

and matching included date of call, gender and age of exposed, state, whether the call was made by a healthcare professional, and severity of medical outcome (Mowry , Spyker , & Cantilena, 2014). As opposed to FDOSS outbreak data, each NPDS record represents one individual, so each record is associated with only one illness. Also, one call may include involve multiple exposures (e.g., when a physician calls to report three separate exposures), which is transcribed as multiple separate NPDS records.

Matching poison center reported exposures to FDOSS outbreaks

I matched NPDS records to outbreaks reported in FDOSS by etiology, state, and call date or date of first reported illness (±7 days) to identify events reported to FDOSS captured by NPDS. Seven days before or after the date of first reported illness was used as the time window for matching as a conservative estimate between onset of a foodborne illness as reported to FDOSS and call to the poison center (Begier, Backer , & Weisman, 2006; Derby, McNally, & Ranger-Moore, 2005). An NPDS record was coded as '1' if the call matched an outbreak reported to FDOSS by etiology, state and date of illness (±7 days) and '0' if the call did not match an FDOSS outbreak.

For sensitivity analysis, matching was also conducted for smaller temporal windows (±1 day, ±3 days, and ±5 days) to see the differences in matching percentage from the 7 day criterion.

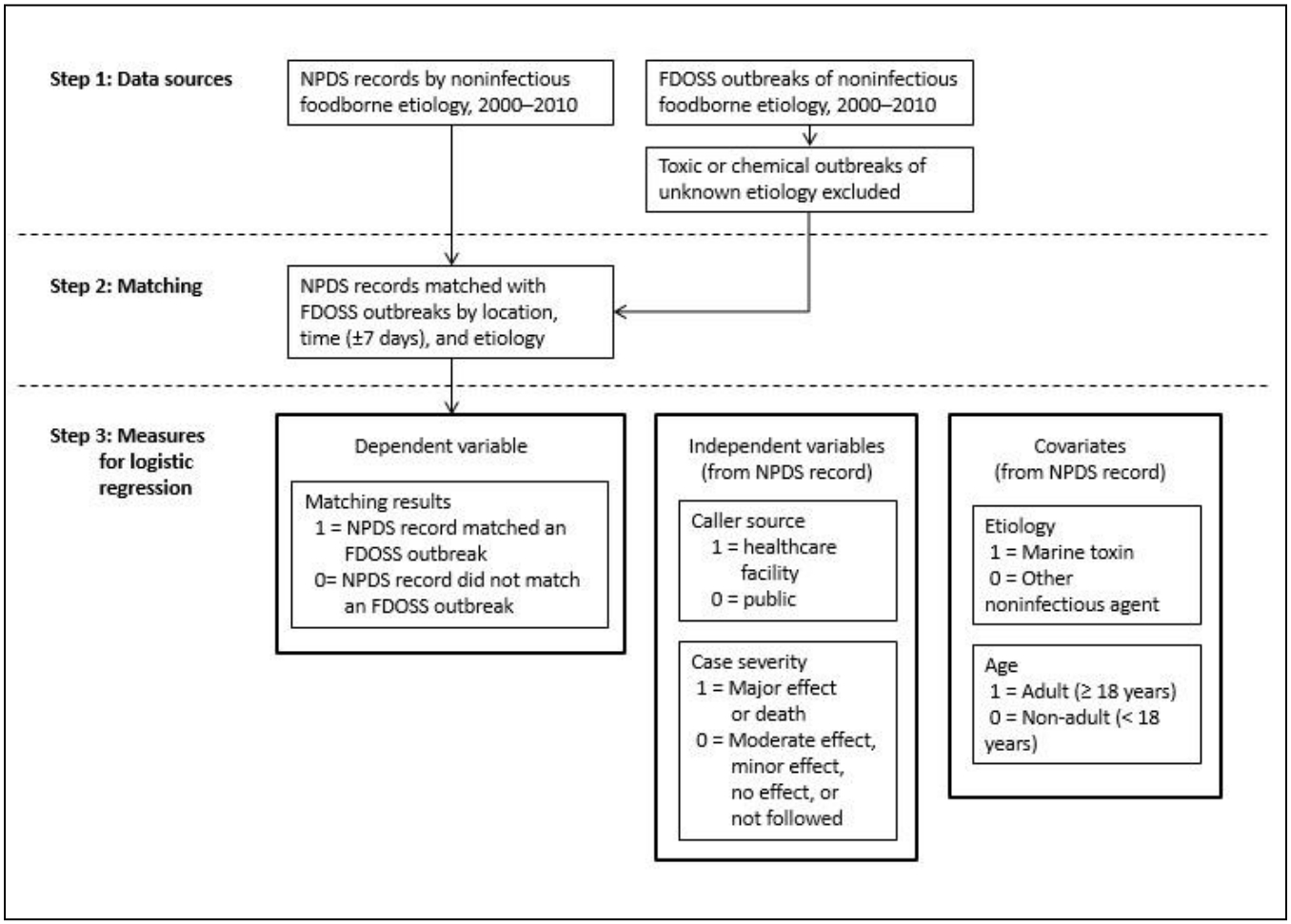
Measures

The dependent variable was the dichotomous variable whether the NPDS record was matched to an FDOSS outbreak by etiology, state and date of illness (±7 days) versus not matched.

There were two main independent variables in the study. The first independent variable was healthcare facility caller as identified in NPDS records, coded as '1' if the call regarding the noninfectious foodborne case originated from a healthcare provider and '0' if the call was from the public. Healthcare facility calls to poison centers are referred to the poison center medical toxicologist for toxicology consultation; reliability of this variable is high. The second independent variable was case severity, which is ascertained by poison center staff in a follow up call after treatment recommendations were given during the initial communication with the poison center. Case severity was defined as 'death', 'major effect' (the patient has exhibited symptoms as a result of the exposure which were life-threatening or resulted in significant residual disability or disfigurement), 'moderate effect' (the patient exhibited symptoms as a result of the exposure which are more pronounced than minor symptoms), 'minor effect' (the patient exhibited some symptoms that were minimally bothersome to the patient), 'no effect' (the patient developed no symptoms as a result of the exposure), and 'not followed' (the patient was not followed because the exposure was likely to result in only minimal toxicity). Poison centers have nationally standardized guidelines for determining case severity so coding of this variable is consistent across all poison centers. A restricted definition of case severity was tested in the model, with 'severe' defined as any reported illness resulting in death or major effect and 'non-severe' defined as any illness resulting in moderate effect, minor effect, no effect, or not followed because minimal health effects expected.

Covariates included etiology and age. Because of the numerous etiology types and different age coding schemes in NPDS, etiology was transformed to a dichotomous variable, which was coded '1' as marine-related (defined as cases related to scombroid toxin, ciguatera

toxin, tetrodotoxin, or PSP) and '0' as non-marine related. Age was transformed to a dichotomous variable 'adult' with patients aged 18 years or older coded as '1' and patients younger than 18 coded as '0'. A flow diagram summarizing the steps to obtain the measures for logistic regression is presented in Figure 2-1.



NPDS = National Poison Data System; FDOSS = Foodborne Disease Outbreak Surveillance System

Figure 2-1. Flow diagram of obtaining measures for logistic regression.

Analytic Approach

I addressed the first objective by assessing the percent concordance of NPDS records with FDOSS outbreaks using temporal, spatial, and etiologic matching. I hypothesized a high percentage of capture of FDOSS outbreaks with NPDS exposures.

I addressed the second objective by using multiple logistic regression on NPDS records to assess the relationship between a NPDS record that matched a confirmed noninfectious FBDO (dependent variable) and healthcare facility caller and case severity (two main independent variables). The specific logistic regression model fitted to the data was:

Logit (NPDS and FBDO match versus not matched) = $b_0 + b_1$(Healthcare facility) + b_2(Severity) + b_3(Etiology) + b_4(Age)

Where b_0 is a constant, and $b_1,\ldots b_4$ are logistic regression coefficients or estimates for the parameters, $\beta_1,\ldots\beta_4$.

The hypothesis was calls to poison centers from healthcare facilities instead of the public may be more indicative of a reported noninfectious FBDO; these calls may have a higher case confirmation accuracy compared to self-reported exposures from the public and healthcare professionals may be more likely to report a potential FBDO to public health authorities (Begier, Backer , & Weisman, 2006). Also, I hypothesized NPDS records where the exposure had a severe medical outcome may be more likely related to a reported noninfectious FBDO since these exposures may more likely to initiate emergency and public health response.

Covariates and interactions between predictors were tested in the model. Model selection was determined using the Akaike information criterion (AIC) (Agresti, 2007). Odds ratios were calculated for predictors in the model with 95% confidence interval. The Hosmer-Lemeshow test was used to assess goodness of fit. Collinearity diagnostics were performed to ensure no multicollinearity existed amongst predictors. A p-value 0.05 was considered significant and all analyses were conducted using SAS 9.3 (SAS Institute, Cary, NC).

2.3 Results

Characteristics of FDOSS outbreaks

From 2000–2010, 614 noninfectious FBDOs were captured in FDOSS. Of these, 80.0% (491 of 614) had a known etiology. Most outbreaks of known etiology were due to scombroid toxin (58.5%, 287 of 614) or ciguatera toxin (32.3%, 159 of 614). The median outbreak size was 3 (range: 2–166) estimated persons ill per outbreak.

Characteristics of NPDS exposure calls

From 2000–2010, 8,773 records of noninfectious FBDO were captured in NPDS. Of these, 24% (2,124 of 8,773) involved an exposure to scombroid toxin and 21% (1,143 of 8,773) to paralytic shellfish poison (Table 2-1). Most callers were from the public (80.6%, 7,071 of 8,773) as opposed to from a healthcare facility (19.0%, 1,702 of 8,773). For case severity, most reports were not followed by the poison center because the exposure was likely due to only minimal toxicity (47.8%, 4,193 of 8,773).

Results from matching FDOSS outbreaks to NPDS records

Among NPDS records, 5% (468 of 8,773) were matched to a confirmed noninfectious FBDOs reported to FDOSS. These records represented 31% (188 of 614) of outbreaks in FDOSS. Among matched NPDS records, scombroid toxin and ciguatera toxin accounted for 53% (248 of 468) and 35% (162 of 468) of records, respectively (Table 2-2).

Matching using smaller temporal windows showed 56.4% 79.1%, 91.5% of NPDS records that matched in the 7-day window also matched the 1-, 3-, and 5-day windows, respectively (Table 2-3). Descriptive statistics of variables in NPDS records stratified by matching are shown in Table 2-4.

Of the 426 outbreaks in FDOSS which did not match to a NPDS record, 20% (124 of 426) involved etiologies such as an unspecified brand of cleaning agents for which no corresponding exposure code in NPDS could be identified.

Results from logistic regression analysis

The multivariable logistic regression model selection indicated statistically significant ($p \leq 0.05$) predictors of concordance of NPDS and FDOSS: severity, healthcare facility caller, etiology, and age. There was a significant association between the severity of the illness called to the poison center and the exposure record being matched to a confirmed FBDO in FDOSS ($p=0.0019$). Calls related to a more severe case have a much higher odds to be related to a noninfectious FBDO than calls related to a less severe care (OR: 2.39; 95% CI: [1.39, 4.13]). There was a statistically significant association between a healthcare facility calling the poison center and the exposure record being matched to a confirmed FBDO in FDOSS ($p<0.0001$). Calls originating from a healthcare facility have a much higher odds to be related to a noninfectious FBDO than calls originating from the public (OR: 2.95; 95% CI: [2.73, 3.68]). There was also a statistically significant association between marine toxin-related exposures and the record being matched to a confirmed FBDO ($p<0.0001$). Calls related to marine-toxin exposures have a much higher odds to be related to a noninfectious FBDO than calls not related to a marine toxin exposure (OR: 19.53; 95% CI: [11.91, 32.02]).The odds ratios and 95% confidence intervals of independent variables are reported in Table 2-5.

All model predictor condition indices were low (1 to 4), suggesting no collinearity in the model predictors. The Hosmer-Lemeshow goodness of fit test suggested good fit ($p = 0.369$).

2.4 Discussion

In this study, I examined whether NPDS records can be used for surveillance of noninfectious FBDOs by comparing noninfectious foodborne-related calls to confirmed noninfectious FBDO events collected by FDOSS. Over the ten-year study period, we found that NPDS records matched with 31% of noninfectious outbreaks reported to FDOSS by location, etiology, and time. These findings suggest that NPDS does capture a significant percentage of noninfectious foodborne outbreak events and illnesses. These findings are consistent with Derby and colleagues (2005) that NPDS records can be used for timely surveillance of infectious foodborne illnesses. Although NPDS records represent only individual reported exposures or illnesses and may not be indicative of an outbreak, the specificity of data collected and the timeliness of data for public health utilization allows for public health officials to respond to potential outbreaks sooner than surveillance of other data sources.

The findings from the logistic regression model predictors suggest there are particular features of NPDS records that may be more indicative of a confirmed noninfectious FBDO. NPDS records about marine toxins have much higher odds to be related to a noninfectious FBDO than records to other noninfectious agents, holding other variables constant. Marine toxin exposures are the most common causes of fish-related illness in the US and may be more traditionally attributed to a FBDO, resulting in actions that may more likely initiate public health response (Pennotti, Scallan, & Backer, 2013). As hypothesized, NPDS records resulting in more severe outcomes have higher odds to be related to a noninfectious FBDO than records resulting in less severe outcomes. Also as hypothesized, NPDS records called by the healthcare facility have higher odds to be related to a noninfectious FBDO than those called by the public.

Although clinical validation is necessary to determine the exact etiology and confirm illnesses called to poison centers and determine whether the case warrants public health investigation, our analysis suggests marine toxin exposure calls, severe outcome calls, and calls made by the healthcare facility should be particular features that public health officials should focus on when conducting surveillance for noninfectious FBDOs using NPDS records. Additionally, using these features to retroactively identify subsets of NPDS records with noninfectious foodborne etiology that did not match an FDOSS outbreak may plausibly identify suspect cases of noninfectious foodborne illness and noninfectious FBDOs that were not reported to FDOSS.

Public health officials may not have the resources to investigate every poison center call with a noninfectious source. This is an important point considering our study found that although NPDS captured many FBDOs reported to FDOSS, only 5% of NPDS records were matched to an event in FDOSS and ninety five percent of NPDS records with noninfectious foodborne etiology were not related to a confirmed event. While the NPDS records not related to a confirmed event may be sporadic cases of noninfectious foodborne disease or clusters of cases related to a FBDO not captured by FDOSS, they could also be calls from the public with unrelated or unconfirmed illness that should not warrant further public health action. Such a high percentage of records potentially not related to a noninfectious FBDO may affect the timing, efficiency, and effectiveness of public health response using NPDS. Careful consideration should be made for determination of the types of NPDS records that may be indicative of a noninfectious FBDO and warrant further investigation. The results from this study provide information on features of calls more likely associated to a confirmed noninfectious FBDO and a framework for assessing which types of calls public health officials

may want to investigate further. More work is needed to identify other features of calls such as reported signs and symptoms which may further narrow the scope of calls for investigation.

Noninfectious foodborne illnesses are regularly reported in calls to poison centers. While frequently reported, these represent a fraction of all illnesses as only a small subset of the US population seeks medical care by calling a poison center. Alternatively for an illness to be reported to FDOSS, the illness must be a part of an outbreak that is recognized and reported to public health authorities. Because noninfectious FBDOs, particularly marine toxin outbreaks, typically affect a small number of people, they may be hard to detect and will therefore be unreported to FDOSS. Thus, both systems have their own limitations to representativeness. This study focused on validating NPDS by assessing its ability to capture FDOSS outbreaks, but based on the two system's inherent limitations it is likely that both surveillance systems are capturing different populations and different FBDOs. The potential complementarity of the two surveillance systems is depicted in Figure 2-2. While each individual surveillance system may capture a different subset of all noninfectious foodborne illnesses in the US, quantifying the capture and overlap of the two systems is critical to understanding how both systems fit in identification of and response to noninfectious FBDOs. Further studies are necessary to assess surveillance system representativeness and to assess how best utilize NPDS for noninfectious foodborne surveillance.

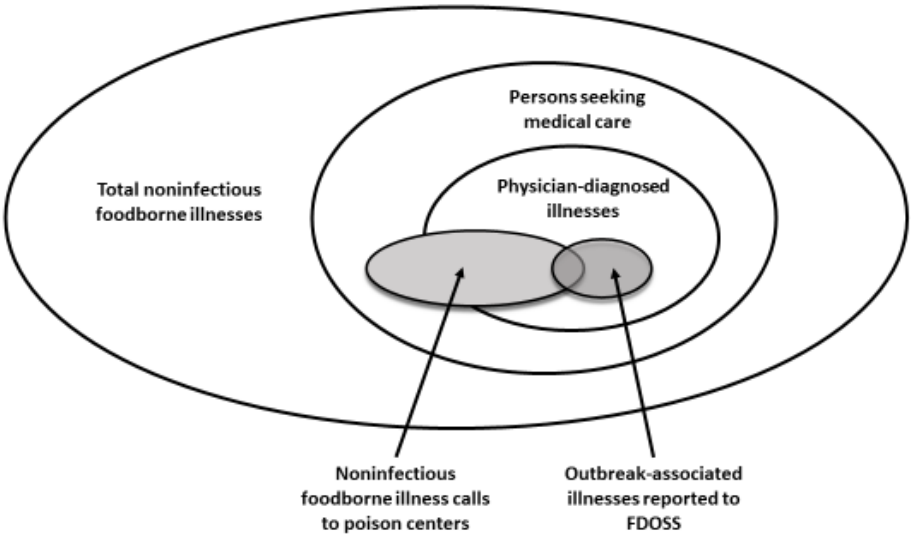


Figure 2-2. Schematic of total foodborne illnesses due to noninfectious agents and the proportion of illnesses reported to poison centers and the Foodborne Disease Outbreak Surveillance System (FDOSS). Adapted from (Pennotti, Scallan, & Backer, 2013).

Since FDOSS only captures the first date of illness onset, the study matching criteria NPDS records received more than 7 days after the earliest onset date would not temporally match the outbreak. Because many noninfectious etiologies, including scombroid toxin and ciguatera toxin, have short times between ingestion and onset of clinical symptoms, it is not surprising that NPDS received more than 50% of records within 1 day of the earliest illness onset date captured in FDOSS (Derby, McNally, & Ranger-Moore, 2005). However, outbreaks involving etiologies such as chronic heavy metal exposure may warrant a longer window of time for NPDS records and it may be more appropriate to tailor the exposure window to each etiology of interest.

This is one of the first analyses assessing the ability for NPDS to capture noninfectious FBDOs by linking two national noninfectious FBDO surveillance systems. There are several limitations to our analysis. Since noninfectious outbreaks tend to be small in size, they may not

be detected or investigated by health departments and thus were not included in this analysis (Pennotti, Scallan, & Backer, 2013). Alternatively, sporadic cases of noninfectious disease may be more common than outbreak-related cases since illnesses may involve exposure of a single person to a discrete contaminated food (e.g. a single fish with high levels of scombroid toxin). Since the analysis was limited by matching NPDS records to outbreaks on the basis of etiology, state and date of call, we cannot conclude that identified NPDS records were definitively linked to an FDOSS outbreak. Moreover, many records in NPDS rely on self-reported data from an exposed person or family member and are not confirmed exposures.

Despite these limitations, NPDS is a potential source of near-real time surveillance data to detect non-infectious foodborne illnesses and outbreaks. Further work is needed to determine how best to identify records most likely to indicate an outbreak.

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Table 2-1. Etiology of outbreaks reported to the Foodborne Disease Outbreak Surveillance System (FDOSS) and exposure calls to the National Poison Data System (NPDS).

Etiology	**FDOSS outbreaks**	**NPDS exposure calls**
	N (%)	N (%)
Total	491	8773
Scombroid toxin	287 (58.5)	2124 (24.2)
Ciguatera toxin	159 (32.4)	1143 (13.0)
Amanita	18 (3.7)	621 (7.1)
Paralytic shellfish poison	12 (2.4)	1827 (20.8)
Heavy metals	10 (2.0)	1371 (15.6)
Tetrodotoxin	2 (0.4)	126 (1.4)
Methomyl	2 (0.4)	203 (2.3)
Monosodium glutamate	1 (0.2)	1358 (15.5)

Table 2-2. Etiology of outbreaks and estimated persons ill reported to the Foodborne Disease Outbreak Surveillance System (FDOSS) and exposure calls the National Poison Data System (NPDS) after matching by etiology, location, and time.

Etiology	**FDOSS**	**NPDS**
	Outbreaks	**Exposure calls**
	N (%)	N (%)
Total	188	468
Scombroid toxin	102 (54.3)	249 (53.1)
Ciguatera toxin	69 (36.7)	162 (34.5)
Paralytic shellfish poison	9 (4.8)	40 (8.5)
Amanita	6 (3.2)	15 (3.2)
Monosodium glutamate	1 (0.5)	2 (0.4)
Tetrodotoxin	1 (0.5)	1 (0.2)

Table 2-3. Matching based on changes in temporal proximity of Foodborne Disease Outbreak Surveillance System (FDOSS) first-reported illness date and National Poison Data System (NPDS) call date with outbreaks and NPDS calls matched by etiology, location, and time.

Etiology	**Matched outbreaks in FDOSS**	**Matched NPDS records**
Total	188	468
± 5 days	171	428
± 3 days	152	370

± 1 days	108	264

Table 2-4. Characteristics of exposure calls in the National Poison Data System matched to a noninfectious outbreak reported in the Foodborne Disease Outbreak Surveillance System.

	Matched	**Unmatched**	**Total**
Characteristic	N (%)	N (%)	N (%)
Total	468	8305	8773
Etiology			
Amanita	15 (3.2)	606 (7.3)	621 (7.1)
Ciguatera toxin	162 (34.5)	981 (11.8)	1143 (13.0)
Methomyl	0	203 (2.4)	203 (2.3)
Monosodium glutamate	2 (0.4)	1356 (16.3)	1358 (15.5)
Heavy metals	0	1371 (16.5)	1371 (15.6)
Paralytic shellfish poison	40 (8.5)	1787 (21.5)	1827 (20.8)
Scombroid toxin	249 (53.1)	1875 (22.6)	2124 (24.2)
Tetrodoxin	1 (0.2)	125 (1.5)	126 (1.4)
Outcome			
Death	0	21 (0.3)	21 (0.2)
Major effect	18 (3.8)	138 (1.7)	156 (1.8)
Moderate effect	152 (32.4)	1411 (17.0)	1563 (17.8)
Minor effect	121 (25.8)	1992 (24.0)	2113 (24.1)
No effect	14 (3.0)	715 (8.6)	729 (8.3)
Not followed / unable to be followed	164 (35.0)	4027 (48.5)	4191 (47.8)
Caller			
Non-healthcare professional	322 (68.7)	6749 (81.3)	7071 (80.6)
Healthcare professional	146 (31.1)	1521 (18.3)	1667 (19.0)
Unknown	1 (0.2)	34 (0.4)	35 (0.4)
Gender			
Male	205 (43.7)	3927 (47.3)	4132 (47.1)
Female	217 (46.3)	4257 (51.3)	4474 (51.0)
Unknown	47 (10.0)	120 (1.4)	167 (1.9)
Age category (years)			
0 to 18	35 (7.5)	1701 (20.5)	1736 (19.8)
Greater than 18	331 (70.5)	5205 (62.7)	5536 (63.1)
Unknown	103 (22.0)	1398 (16.8)	1501 (17.1)

Table 2-5. Logistic regression model parameter estimates and odds ratios for matching NPDS records to an outbreak reported to the Foodborne Disease Outbreak Surveillance System (FDOSS).

Outcome: matching an FDOSS outbreak	**Regression Coefficient**	**Chi-square**	**P-value**	**Odds ratio (95% CI)**
Intercept	-6.115	460.475	<0.0001	-
Outcome severity	0.870	9.670	0.0019	2.386 (1.379, 4.127)
Healthcare facility caller	1.083	94.095	<0.0001	2.953 (2.373, 3.676)
Marine etiology	2.972	138.845	<0.0001	19.531 (11.913, 32.020)
Age	0.482	7.619	0.0058	1.619 (1.150, 2.279)

Chapter 3: Effect of Prescription Drug Monitoring Program Implementation on Opioid- and Heroin-associated Exposures Called to Poison Centers

3.1 Introduction

Prescription opioid abuse is the intentional, non-medical use of an opioid to obtain a euphoric or psychotropic effect. Abuse of prescription opioids is a substantial public health problem in the United States (US); an estimated 1.9 million people suffered from substance abuse related to prescription opioids in 2013. An estimated sixteen thousand people died in the US due to prescription opioid medications in 2010 (Dart, Surratt, & Cicero, 2015; SAMHSA, 2014).

Many federal regulations such as educational initiatives and abuse-deterrent formulations of opioid analgesics have been implemented to limit abuse of opioids (NIDA, 2016). States have also taken additional legislative actions to reduce opioid abuse by monitoring and controlling the dispensing and prescribing of these substances. One type of intervention cited as having significant potential in reducing opioid abuse and misuse is prescription drug monitoring programs (PDMPs). PDMPs use statewide electronic databases that collect prescription data from prescribers and dispensers on medications classified as federal controlled substances. Programmatic details differ among states, but PDMPs are designed to assist in detecting and preventing abuse, misuse, and diversion of controlled substances. Specifically, programs are targeted toward reducing the incidence of 'doctor shopping' which occurs when patients see multiple providers and pharmacies with the intent of obtaining controlled substances for misuse (Blumenschein, Fink, & Freeman, 2010). As of 2015, 49 states have enacted laws allowing for creation of PDMPs (NAMSDL, 2014). Many states

already have active programs while some states are in the process of implementing programs and initiating data collection; lack of state funding towards these programs oftentimes hinders or delays implementation.

Many national studies using a variety of data sources have sought to assess whether PDMPs have affected morbidity and mortality attributable to opioid abuse. Simeone and Holland (2006) used multilevel modeling of prescription drug shipments in states with and without PDMP implementation to show that per capita supply of prescription pain relievers to PDMP states decreased after implementation of the PDMP and in doing so reduced the probability of abuse by users for these drugs. A follow-up study showed decreases in supply of prescription drugs found in states with active PDMP programs were associated with lower rates of opioid-related admissions to emergency departments (Reismann, Shenoy, & Atherly, 2009). Reifler, Droz, and Bailey (2012) studied pre- and post-implementation of PDMP in an aggregated number of states and found opioid abuse rates in the population was reduced after implementation.

States have yet to publish well designed quasi-experimental studies on the effectiveness of PDMPs on opioid-related illnesses and deaths resulting from abuse. State PDMP data have been shown to change doctor prescribing behavior once providers are able to access a patient's information in a PDMP database (Baeren, Marco, & Droz, 2010). A few states have evaluated PDMP performance using end-user satisfaction surveys, but have not yet tied these evaluations to changes in opioid abuse trends (PDMP evaluations, 2016). While these studies suggest the possible effects of PDMP implementation on opioid abuse, there are no state-level studies examining the impact of PDMPs on opioid abuse rates. Surveys to states have noted that more

state-specific studies of the effect of PDMP implementation on the opioid epidemic are recommended to justify continued funding and implementation (Katz & Houle, 2008).

Moreover, no studies have examined the relationship between prescription opioid abuse and heroin use at the state level. An estimated 517,000 people suffered from a heroin use disorder in 2013 (SAMHSA, 2014). Research suggests almost half of young people who inject heroin reported abusing prescription opioids before starting to use heroin. These individuals reported switching to heroin because it is cheaper and easier to obtain than prescription opioids (Cicero, Ellis, & Surratt, 2012; Pollini, Banta-Green, & Cuevas-Mota, 2011). One of the potential effects of policies such as PDMP implementation to reduce opioid abuse may be an increase of heroin use as individuals choose an alternative once doctor shopping for opioids becomes regulated (Dart, Surratt, & Cicero, 2015). State-specific studies examining the effect of PDMP implementation on heroin use rates are needed to adequately study and predict the potential negative effects of PDMP implementation.

United States poison centers offer free, confidential medical advice 24 hours a day, seven days a week through a national help line to assist in poison exposures. Call data are transmitted and stored in an electronic database every eight minutes to the National Poison Data System (NPDS), which can be used for near-real-time surveillance for disease conditions or exposures and to provide situational awareness during incidents of public health significance (Wolkin, Martin, & Law , 2012). Poison centers receive calls from both healthcare providers and the public, with 15% of call from healthcare providers and 85% of call from the public (Mowry, Spyker, Cantilena, McMillan, & Ford, 2014). While utilization of poison centers are dependent on demographic characteristics, studies estimate that about seven per thousand population use

poison center services annually (Litovitz & Benson, 2010). Reported exposures include opioid- and heroin-associated symptoms. Previous studies have described opioid- and heroin-related calls to poison centers (Davis, Severtson, & Bucher-Bartelson, 2014; Spiller, Lorenz, & Bailey, 2009). These studies have shown that not only have opioid-related calls increased, but increases in poison center calls related to opioids were correlated with increases in prescription opioid-related emergency department visits. Also, studies have shown that pharmaceutical reformulations of certain opioids to reduce the potential for abuse are correlated with increases in heroin overdoses (Dart, Surratt, & Cicero, 2015). There has yet to be a state-level analysis of PDMP effectiveness using NPDS records. Having a framework for using NPDS records to evaluate state PDMP effectiveness can aid states in generating the critically important information needed to support and improve PDMP operations.

The objective of this study was to use NPDS records to assess whether PDMP implementation is associated with a reduction of opioid-associated calls and an increase of heroin-associated calls. I analyzed a time series of opioid and heroin use and abuse captured by NPDS records, defined in this study as the ratio of monthly opioid- or heroin-associated calls to non-steroidal anti-inflammatory drug-associated calls. This analysis was conducted in one state that implemented a PDMP within the study period compared to a state that did not implement a PDMP during within the study period. The working hypotheses were that 1) trends in opioid-related calls to NPDS would be attenuated upon PDMP implementation but should be unaffected in the absence of PDMP implementation and 2) trends in heroin-related calls to NPDS would increase upon PDMP implementation but should be unaffected in the absence of PDMP implementation.

3.2 Methods

Study Location

Since PDMP implementation occurs at the state level, comparisons can be made within the state (pre- and post-implementation) and between states with and without PDMP programs in place. Two states were chosen as a part of this study. The first state implemented a state-wide PDMP in the winter of 2011 and is the intervention state in this study. To ensure there was enough time series data, twenty four months before and after the date of the intervention state PDMP implementation was chosen as the study period, from November 1, 2009 to October 31, 2013. A second state was chosen which implemented a PDMP after November 2013 outside the study period. This state is geographically close in proximity to the intervention state and was chosen as a control state for this study. Both states have comparable racial and age demographics and similar poison center utilization rates per 100,000 population (Table 1) (Quickfacts, 2016).

Data

NPDS

NPDS captures standardized information on each call received by a poison center including the implicated substance of exposure, patient demographics, and clinical and case management data. Each NPDS record is assigned a specific substance code to identify the substance(s) of exposure and enable surveillance. NPDS users can query the data using a combination of substance codes, clinical data, and health outcomes (Mowry, Spyker, Cantilena, McMillan, & Ford, 2014). For this study, monthly opioid-associated calls were queried from NPDS for the 48-month study period, from November 1, 2009 to October 31, 2013, by state.

Monthly heroin-associated calls and non-steroidal anti-inflammatory drug (NSAID) associated calls were also queried for the study period. Calls included both from healthcare providers and the general public. Calls reporting exposure to multiple substances and calls deemed to be confirmed non-exposures by poison center staff were excluded from the study.

NAMSDL

The National Alliance for Model State Drug Laws (NAMSDL) collects information on state PDMP programs, including date of legislative enactment of PDMP and date of user access to the PDMP (NAMSDL, 2014). All information is reported by the state program that oversees PDMP implementation. Data are collected every two to five years. Information used in the NAMSDL database for this study included the PDMP implementation date, which is defined in this study as the month and year the state PDMP program allowed access to the PDMP by prescribers (physicians) and dispersers (pharmacies).

Measures

There were two primary dependent variables for this study. The first dependent variable was the ratio of opioid-associated records and NSAID-associated records per month for the state. An opioid-associated record was defined as an NPDS record where the patient reported exposure to an opioid. An NSAID-associated record was defined as an NPDS record where the patient reported exposure to an NSAID. For example, if the poison center that services the intervention state received 10 opioid records and 100 NSAID records in a month, then the ratio would be 0.1 opioid-associated exposures per NSAID-associated exposure that month. Using this ratio as the dependent variable has several advantages compared to absolute counts. Poison center utilization varies by time and state so absolute counts or rates by population

would be highly dependent upon the number of people who know about poison centers and choose to use poison centers when seeking healthcare advice. Using a group of substances that would not be affected by PDMP implementation, such as NSAIDs, as a denominator can provide a background rate of calls that addresses changes in overall poison center utilization. This measure allows for a more valid and stable comparison between pre- and post-intervention periods and between states.

The second dependent variable was the ratio of heroin-associated records and NSAID-associated records per month for the state. A heroin-associated record was defined as an NPDS record where the patient reported exposure to heroin.

The independent variable was the implementation of the PDMP in the intervention state defined as the month and year the PDMP allowed user access to the PDMP database. This date was obtained from NAMSDL data.

Analysis

I estimated segmented time series regressions on trends in the opioid to NSAID ratio and the heroin to NSAID ratio over the 48-month study period. Model specification included a constant and terms for: pre-intervention trend in ratio, change in ratio during the intervention month, and change in trend between the pre- and post- intervention periods. First-order autocorrelated errors were assumed in model specification. The specific regression model fitted to the data was:

$$Ratio_t = \beta_0 + \beta_1 * time_t + \beta_2 * intervention_t + \beta_3 * time\ after\ intervention_t + e_t \quad \textit{for the intervention state}$$

Where:

- $Ratio_t$ is the ratio of opioid-associated NPDS records to NSAID-associated NPDS records
- β_0 estimates the baseline ratio at the beginning of the study period
- β_1 estimates the change in ratios that occur with each month during the pre-intervention period
- $Time_t$ is a continuous variable indicating the number of months into the study period. The total study period was 48 months.
- β_2 estimates that change in the ratio immediately following PDMP implementation
- β_3 estimates the change in trend after PDMP implementation compared to the slope before implementation
- Time after $intervention_t$ is a continuous variable indicating the number of months after PDMP implementation. This is coded as zero during the pre-intervention period.
- e_t represents the random error.

An equivalent regression model was specified and estimated for the heroin to NSAID ratio. For the control state an equivalent regression model was specified and estimated for both opioids and heroin. An alpha level of 0.05 was considered significant. The intervention month for the control state was defined as the mid-point of the 48 month time series (October 2011).

We hypothesized that for opioids: 1) the ratios would not significantly decrease each month among both states during the pre-intervention period, 2) the ratios in the intervention month would not significantly decrease and the pre-intervention trend will be sustained in the post-intervention period for the control state with no PDMP implementation (control state), and 3) the ratio in the intervention month would significantly decrease and the pre-intervention trend will be attenuated in the post-intervention period for the state with PDMP implementation (implementation state).

We hypothesized that for heroin: 1) the ratios would not significantly change each month among both states during the pre-intervention period, 2) the ratios in the intervention

month would not significantly increase and the pre-intervention trend will be sustained in the post-intervention period for the control state, and 3) the ratio in the intervention month would significantly increase and the pre-intervention trend will increase in the post-intervention period for the intervention state.

Data management and analysis were performed in SAS 9.3 (SAS Institute, Cary, NC).

3.3 Results

Opioids

There were a total of 1,312 opioid-associated calls in state A and 770 in the control state during the study period. There were a total of 14,253 NSAID-associated calls in the intervention state and 9,442 in the control state. The monthly opioid ratio for the intervention state ranged between 0.052 and 0.125 opioid records per NSAID record with a median of 0.087. The monthly opioid ratio for the control state ranged between 0.042 and 0.128 opioid records per NSAID record with a median of 0.083. The ratio of opioid to NSAID records was highest in the month of August 2011 for the intervention state and June 2010 for the control state. The monthly ratios of opioid ratios and heroin ratios for both states during the study period are displayed in Figure 3-1.

The time series regression estimates and 95% confidence intervals of opioid to NSAID ratio per month for the two time series are displayed in Figure 3-2. In the 24-month pre-intervention period, there was some variability between the trends seen between states. The ratio increased by 0.001 per month for the intervention state ($p<0.001$) while the ratio decreased by -0.0004 per month for the control state ($p<0.001$). These estimates suggest that

during the pre-intervention period, the intervention state had an increasing ratio of opioid calls to NSAID calls while the control state had a slightly decreasing ratio.

The pre-intervention trend of opioid to NSAID ratios was significantly attenuated in the post-intervention period for the intervention state. While the trend in the intervention state was an increase of 0.001 per month in the pre-intervention period, the trend was a decrease of -0.002 per month in the post-intervention period ($p<0.001$), which yielded a net loss of -0.001 per month following intervention. Because of this, the post-intervention trend in the intervention state declined during the rest of the study period.

The effect of PDMP implementation in the intervention state on the opioid to NSAID ratio was immediate. In the PDMP implementation month (month 25), the intervention state saw a -0.017 decrease in the ratio ($p <0.001$, Figure 3-2). This effect was not seen in the non PDMP implementation state; the control state saw a 0.003 increase in the ratio and this estimate was not statistically significant ($p=0.13$).

Alternatively similar trends were not found in the control state. The effect size of all three estimates (pre-intervention trend, implementation month change, and post-intervention trend) was comparatively small so the overall trend of the opioid to NSAID ratio stayed relatively constant throughout the study period. The trend in the control state was a decrease of -0.0004 per month in the pre-intervention period ($p<0.001$) and an increase in 0.0007 per month in the post-intervention period ($p<0.001$). Figure 3-3 displays the observed 48-month trends in opioid ratio and the pre-intervention trends (months 1-24) projected into the post-intervention study period for the intervention state. Twenty-four months after PDMP

implementation, the observed ratio was 47.2% less than the projected ratio. For the control state, the observed ratio was higher than projected.

Heroin

For heroin-associated calls, there were a total of 188 in the intervention state and 202 for the control state. The heroin ratio for the intervention state ranged between 0.003 and 0.047 heroin records per NSAID record with a median of 0.013. The heroin ratio for the control state ranged between 0.004 and 0.063 with a median of 0.022. The ratio of heroin to NSAID records was highest in the month of September 2013 for both states (Figure 3-1).

The heroin ratio trends were very similar between states in the 24-month pre-intervention period. The ratio increased by 0.00007 per month for the intervention state ($p=0.52$) while the ratio increased by 0.0003 per month for the control state ($p<0.001$). These estimates suggest that during the pre-intervention period, both states had a very slightly increasing ratio of heroin calls to NSAID calls.

The pre-intervention trend of heroin to NSAID ratios was significantly increased in the post-intervention period for the intervention state. While the trend in the intervention state was a slight increase of 0.00007 per month in the pre-intervention period, the trend was an increase of 0.0008 per month in the post-intervention period ($p<0.001$). Because of this, the post-intervention trend in the intervention state increased during the rest of the study period.

Alternatively we did not see similar trends in the control state. While the trend in the control state was a slight increase of 0.0003 per month in the pre-intervention period, the trend was a slight decrease of -0.0003 per month in the post-intervention period ($p<0.001$).

Figure 3-3 displays the observed 48-month trends in heroin ratio and the pre-intervention trends (months 1-24) projected into the post-intervention study period for the intervention state. Twenty-four months after PDMP implementation, the observed ratio was 136% more than the projected ratio. For the control state, the observed ratio was lower than projected.

3.4 Discussion

The objective of this study was to use NPDS records to assess whether PDMP implementation is associated with a reduction in the time trend of opioid-associated calls and an increase in time trend of heroin-associated calls. Instead of absolute counts I used ratios of NPDS records to account for differences in poison center utilization and population over time and between states. For comparison, I observed trends in a state with PDMP implementation and a neighboring state with no PDMP implementation within the 48-month study period.

The intervention state significantly attenuated the expected trend of rising opioid trends following implementation of the PDMP. The effect was immediate as evidenced by the ratio decrease in the month following implementation. Moreover, the effect persisted during the rest of the study period as the trend sloped downward in the months following implementation. When I projected the pre-intervention trend into the post-intervention period for the intervention state, I found the projected ratio in the last month of the study period to be almost twice as high as what was observed. These findings suggest that if NSAID calls remained relatively stable during the study period, there would be an expected twice as many opioid-related NPDS records in the last month of the study period had the intervention state not implemented a PDMP. While there have not been similar studies at the individual state level,

these findings corroborate studies at the national level that opioid-related calls decrease after PDMP implementation (Reifler, Droz, & Bailey, 2012). Alternatively, the control state did not see similar decreases in the post-intervention period. The absence of a similar trend in the control state suggests that the decreases in trend following PDMP implementation in the intervention state were unlikely due to other external factors that would also affect the control state, such as national opioid drug reformulations put in place to reduce opioid abuse (Coplan, Kale, & Sandstrom, 2013).

However, decreased opioid trends following implementation seen in the intervention state were also associated with increases in heroin trends. The intervention state saw an increase in heroin trends following PDMP implementation and this effect persisted during the rest of the study period. When projecting the pre-intervention trends into the post-intervention period for the intervention state, the heroin to NSAID ratio was twice the amount as what was projected in the last month of the study period. Just as there would be an expected twice as many opioid-related records if the intervention state had not implemented a PDMP, there would be half as many heroin-related records in the absence of a PDMP. These results when paired with trends seen in opioids in the intervention state suggest there may have been a substitution effect of individuals switching to heroin once doctor shopping for opioids becomes a less available option. These findings corroborate national studies looking at substitution of heroin for opioids as accessibility of opioids decreases (Dart, Surratt, & Cicero, 2015). More studies are needed to assess the amount of substitution to expect when implementing policies and programs that decrease the availability of obtaining opioids for abuse.

There are policy implications for the findings in this study. Evaluation of the effects of PDMP implementation provides the necessary context and evidence for federal and state legislators to make sound public health decisions on addressing the opioid and heroin epidemic. This is timely as the US Congress hopes to pass a bill to combat the prescription opioid and heroin epidemic for fiscal year 2017 (New York Times , 2016). Moreover, public health officials should prepare for the substitution of opioid abuse to heroin use suggested in this study upon implementation or enhancement of state PDMPs.

In this study, it was demonstrated that a quasi-experimental time series design using a comparison group on NPDS records could be used to assess the effects of state intervention policies and programs. This type of study design was also rigorous enough to rule out many factors other than the PDMP implementation that would have led to changing trends. I also created a new measure – the ratio of records in NPDS – that adjusts for many different factors such as poison center utilization and changing population rates that can account for variation in monthly absolute counts of opioid- and heroin-associated records.

Using segmented time series designs to study NPDS records may improve the ability to assess and detect subtle trends such as the effect and effectiveness of interventions. Syndromic surveillance data such as NPDS records are typically analyzed using traditional aberration detection methods. Techniques include statistical process control such as the historical limits method and change point analyses (Fricker, 2013). The sensitivity, specificity, and timeliness of detection for different techniques vary significantly and depend widely upon the desired focus of the researcher. Consequently, many of these techniques are only effective for detecting sudden major changes in time series data and have limited ability to identify subtle and

potentially important changes in time series trends. Detecting changes in trend using techniques like segmented time series could be a critical tool to inform public health decision-making. This study provides a basic framework for study design and how to create valid measures for future studies examining changing trends from state-level interventions using NPDS records.

There are several limitations to the study. For opioids, the trends for the intervention and control states were not similar prior to PDMP implementation which may suggest that the comparison state was not experiencing similar opioid use trends during the pre-intervention period. Moreover, there may be some unmeasurable interaction between the states not taken into account in this study. In particular, it is plausible that stricter prescription opioid abuse policies like implementation of PDMPs in one state may drive opioid abusers to neighboring states with less strict opioid prescribing in the absence of a PDMP. This phenomenon, while not specifically studied, is similar to switching from prescription opioid abuse to heroin abuse when stricter opioid regulations are enacted. If the slight increases in opioid to NSAID ratios seen in the control state in the post-intervention may be partially accounted for by decreases in opioid ratio in the intervention state, then the comparison between states overestimates the effect of PDMP implementation on opioid to NSAID ratios seen in the intervention state. Further studies using multiple states as controls may explain whether this phenomenon is present in this study.

The immediate and persistent effects of PDMP implementation on the opioid to NSAID ratios in state A suggest that PDMP implementation does affect opioid abuse rates at the state level. The associated increases in heroin to NSAID ratios following PDMP implementation suggest a substitution effect is present as availability of prescription opioids for abuse declines.

The approaches in this paper provide a framework for detecting changing trends in NPDS records for assessment of public health interventions such as PDMP implementation. Future research should focus identifying particular features of state PDMPs that are more effective in contributing to decreasing opioid abuse trends.

3.5 References

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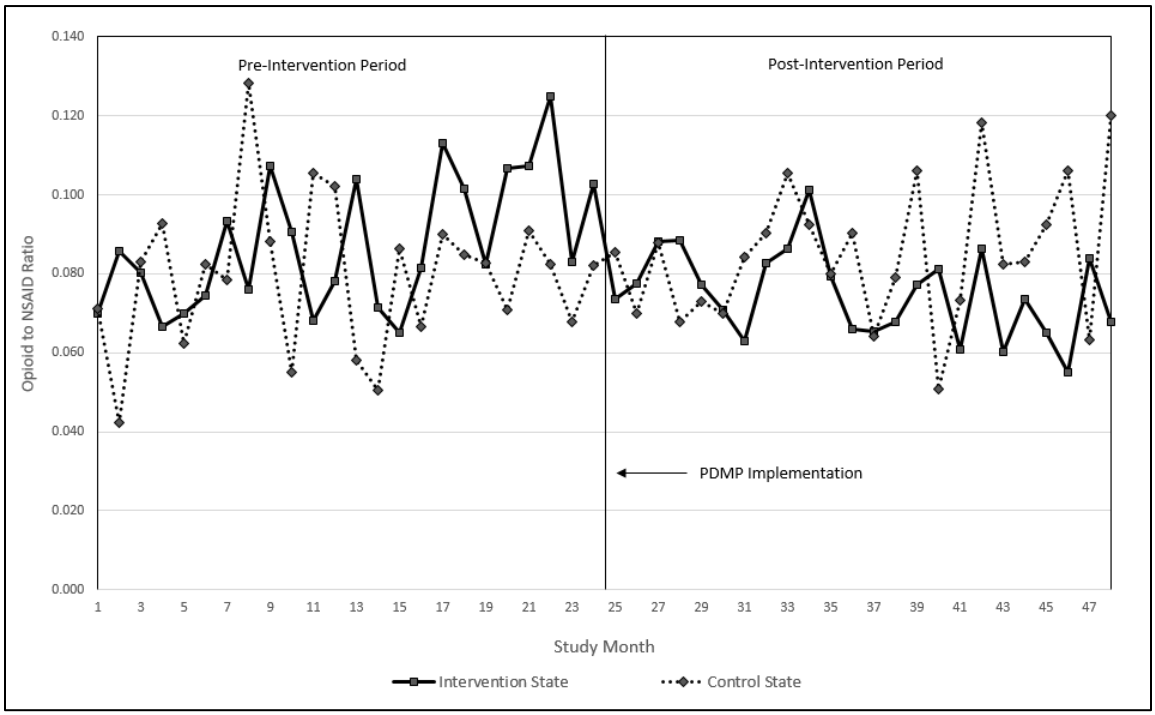
Table 3-1. Demographic and Poison center utilization characteristics of states in the study.*

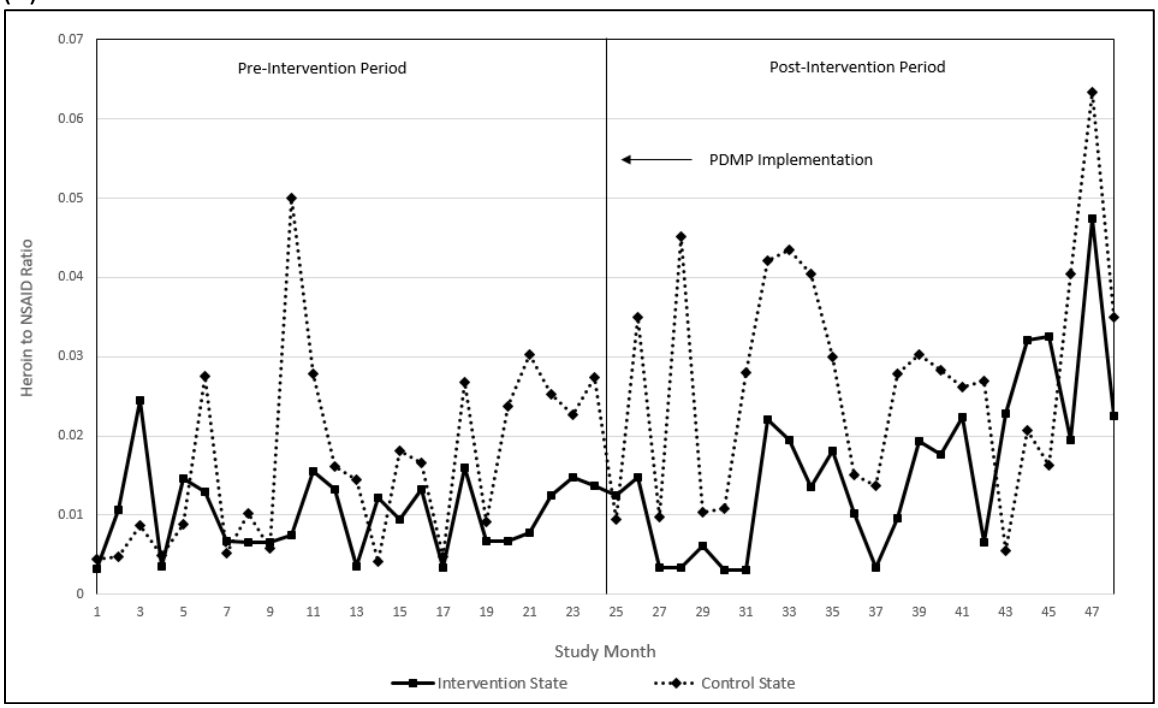
State Characteristic	Implementation state (PDMP state)	Control state (non-PDMP state)
Population	18 million	10 million
Age		
Persons under 5, percent	5.5%	6.6%
Persons over 18, percent	21.3%	24.7%
Race		
White, percent	75.0%	62.1%
Black, percent	17%	30.0%
Economy		
Median household income, dollars	$47,000	$49,000
Persons in poverty, percent	16.5%	18.3%
Total unemployment rate, percent	6.3%	7.1%
Poison center utilization per year (per 100,000 population)	1,005	1,132

*Data obtained from the 2010 United States Census Bureau and Bureau of Labor Statistics.
PDMP = prescription drug monitoring program

(A) Opioid to NSAID ratio



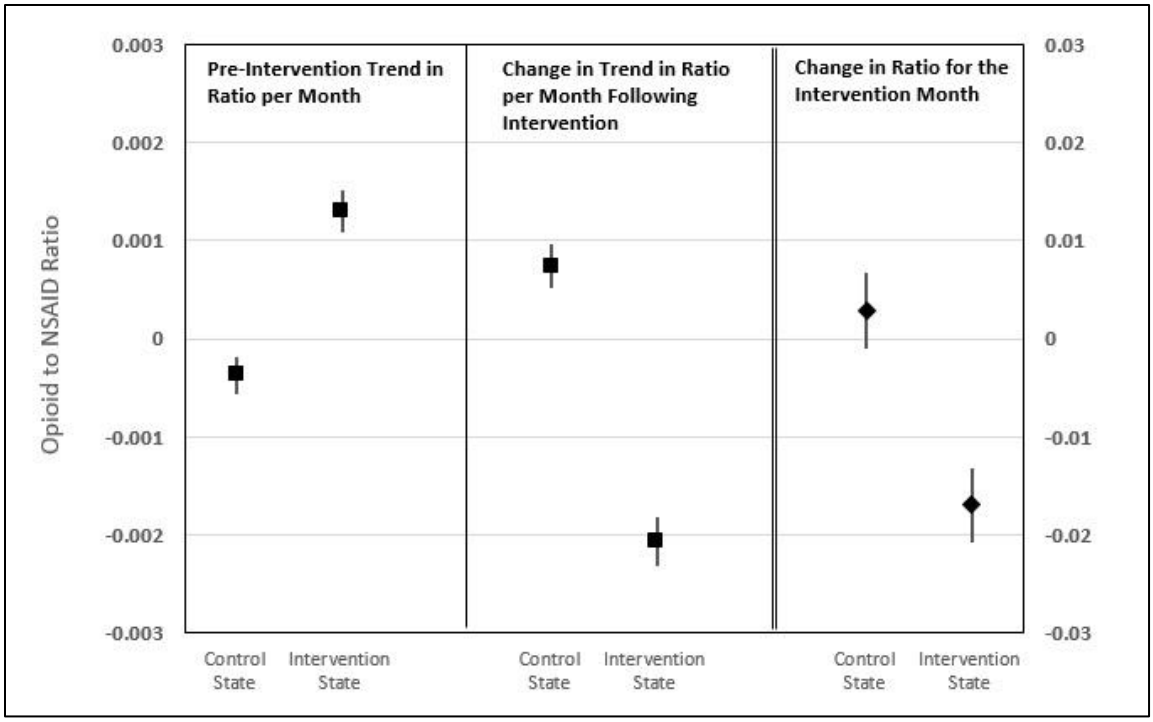
(B) Heroin to NSAID ratio



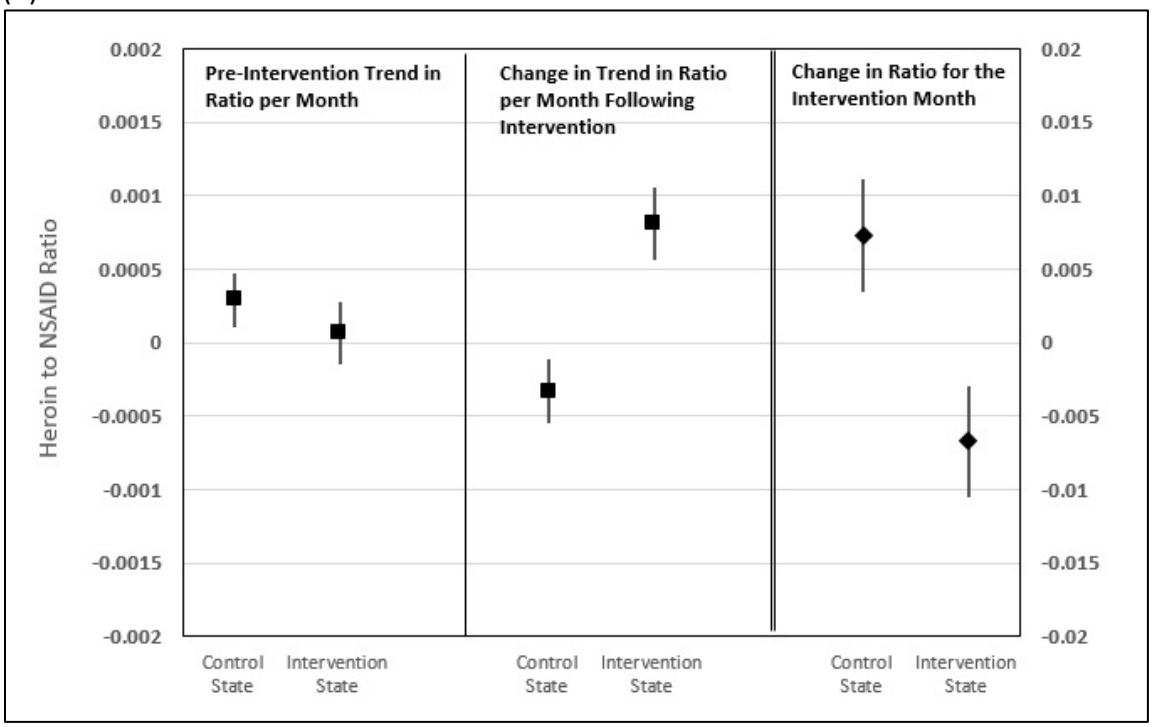
NSAID = non-steroidal anti-inflammatory drug; PDMP = prescription drug monitoring program

Figure 3-1. Observed trends in ratios in a state with prescription drug monitoring program (PDMP) implementation and a state without PDMP implementation over a 48-month study period. (A) Opioid to non-steroidal anti-inflammatory drug (NSAID) ratio. (B) Heroin to NSAID ratio.

(A) Opioid to NSAID ratio

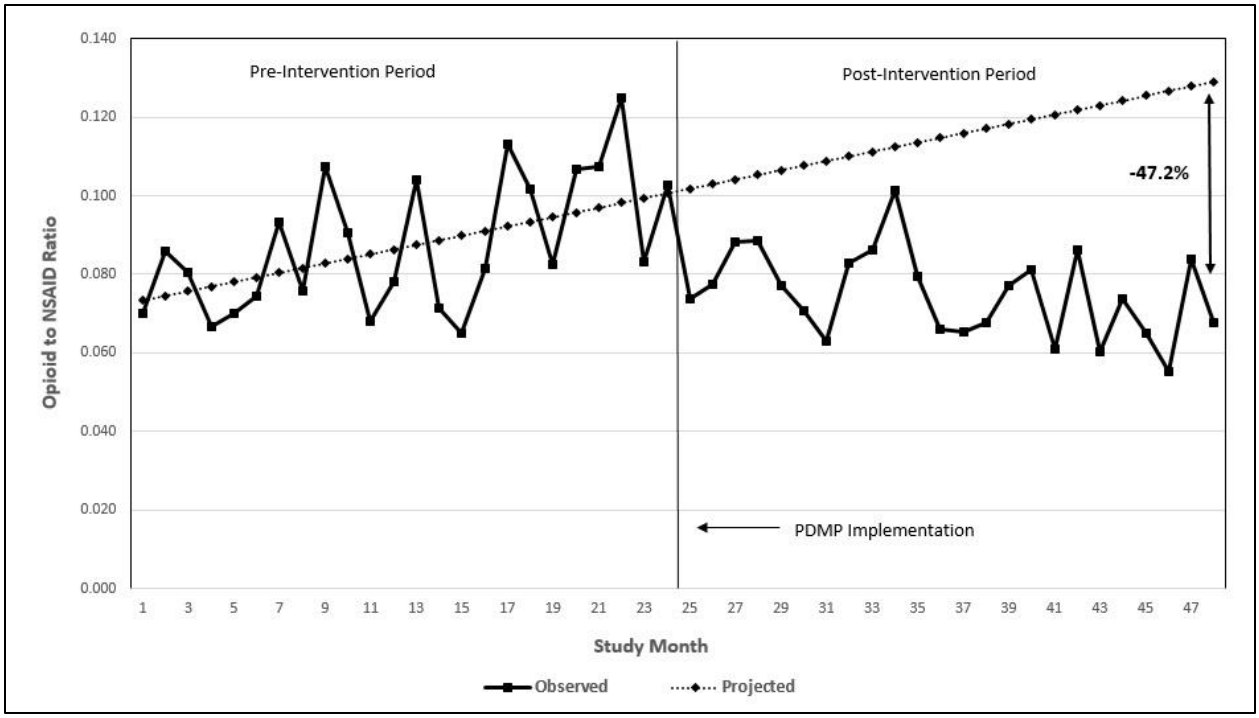


(B) Heroin to NSAID ratio

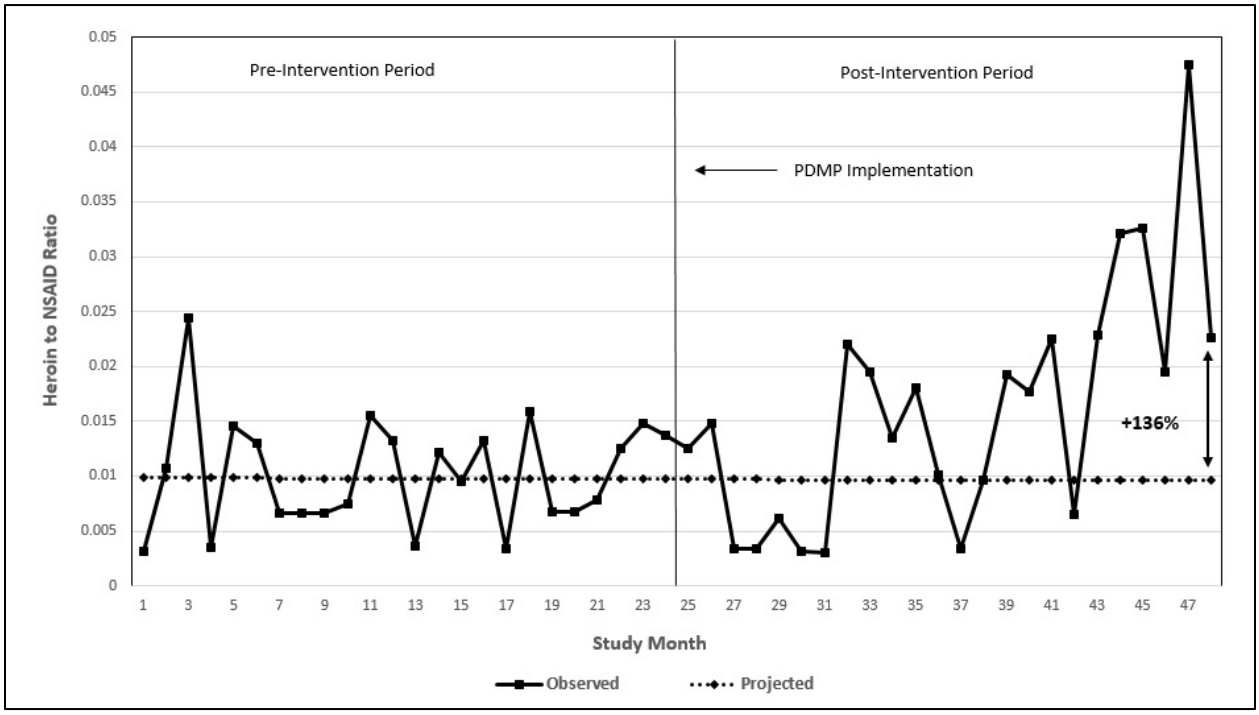


NSAID = non-steroidal anti-inflammatory drug

Figure 3-2. Estimates for the effects of prescription drug monitoring program (PDMP) implementation on (A) opioid and (B) heroin ratios in a state with PDMP implementation and a state without PDMP implementation over a 48-month study period.
(A) Opioid to NSAID ratio



(B) Heroin to NSAID ratio



NSAID = non-steroidal anti-inflammatory drug; PDMP = prescription drug monitoring program

Figure 3-3. Observed trends in ratios and projected trends based on pre-intervention ratios for the state with prescription drug monitoring program implementation. (A) Opioid to non-steroidal anti-inflammatory drug (NSAID) ratio. (B) Heroin to NSAID ratio.

Chapter 4: Effect of State Marijuana Legislation on Marijuana and Synthetic Cannabinoid Use

4.1 Introduction

Marijuana has long been used for its neuropsychiatric effects including enhanced relaxation and perceptual alterations (Green, Kavanagh, & Young, 2003). The primary active ingredient of marijuana is Tetrahydrocannabinol (THC), which binds to the cannabinoid receptors in the body.

Synthetic cannabinoids also bind to the same cannabinoid receptors. These substances were initially created as pharmaceutical agents attempting to mimic the clinical attributes of marijuana and THC. However, synthetic cannabinoids have gained popularity in the past decade as recreational drugs because it is believed use of these substances result in a marijuana-like high.

Synthetic cannabinoids, also called spice or K2, are man-made compounds that are sprayed onto shredded plant material so they can be smoked. These products are often marketed as safe and legal even though the Drug Enforcement Administration has banned the marketing and sale of these substances in the United States (Drug Fact Sheet: Spice, 2016). Despite these bans, synthetic cannabinoid use continues to be popular among youth and has recently been implicated in numerous outbreaks in the United States (Law, Schier, & Martin, 2015; Kasper, Ridpath, & Arnold, 2015; CDC, 2013; CDC, 2013).

Currently, marijuana is still criminalized at the federal level, although there have been piecewise changes at the state level for decriminalization and broadening use of medical and recreational marijuana. Currently, 22 states have passed legislation allowing medical marijuana use. Four states and the District of Columbia have allowed the use of recreational marijuana for

people over 21 years old (Governing Magazine, 2016). Even though there has been fierce political debate on recreational and medical marijuana legalization, there have been few studies looking at the effect of these types of legislation on marijuana use rates. Moreover, the conclusions to published studies were mixed. Two studies showed that marijuana use did not increase in adolescents or adults following legislation on medical marijuana use (Choo, Benz, & Zaller, 2014; Harper, Strumpf, & Kaufman, 2012) while three studies showed that marijuana use increased following medical marijuana legalization (Wang, Roosevelt, & Le Lait, 2014; Cerda, Wall, & Keyes, 2011; Wall, Poh, & Galea, 2011). All of these studies were conducted at the national or multi-state level. There are no published state-specific studies on marijuana use following legalization. These types of studies are critically needed to inform policy-makers of the effects of marijuana legalization on marijuana use rates.

Moreover, there have not been any studies examining the effect of marijuana laws on synthetic cannabinoid use. Because of the similarity of active ingredients, synthetic cannabinoids are often misleadingly called synthetic marijuana, even though studies have shown the adverse effects of synthetic cannabinoids are very different and often more damaging than the effects of marijuana (Forrester, Kleinschmidt, & Schwarz, 2011). One of the main drivers of the popularity of synthetic cannabinoids is that they are not detectable in typical urine drug screens for marijuana and THC (Kirstin & Lauritsen, 2016). A survey of Maryland synthetic cannabinoid users showed that 71% of users cited the main reason for using synthetic cannabinoids was to get high without having a positive drug test (Bonar, Ashrafioun, & Ilgen, 2014). Synthetic cannabinoid users were opting for a more harmful alternative to traditional marijuana to avoid the legal ramifications of marijuana use. Thus, one of the

potential effects of recreational and medical marijuana legalization is the decrease in synthetic cannabinoid use as those who were using synthetic cannabinoids may switch to a legal, regulated, and less harmful alternative to get high. The policy implications of this finding would be substantial considering many state and federal policies and public health interventions have not been able to curb synthetic cannabinoid use.

United States poison centers offer free, confidential medical advice 24 hours a day, seven days a week through a national help line to assist in poison exposures. Call data are transmitted and stored in an electronic database every eight minutes to the National Poison Data System (NPDS), which can be used for near-real-time surveillance for disease conditions or exposures and to provide situational awareness during incidents of public health significance (Wolkin, Martin, & Law , 2012). While utilization of poison centers are dependent on demographic characteristics, studies estimate that about seven per thousand population use poison center services annually (Litovitz & Benson, 2010). Reported exposures include marijuana- and synthetic cannabinoid-associated calls. NPDS records have been used to track national marijuana and synthetic cannabinoid exposure trends (Forrester, Kleinschmidt, & Schwarz, 2011). However, there has yet to be a state-level analysis using NPDS records examining the effects of marijuana laws on marijuana and synthetic cannabinoid use rates. Having a framework for using NPDS records to evaluate the effect of marijuana laws on these substances can aid states in generating the critically important information for planning and responding to the effects of medical and recreational marijuana legalization.

The objective of this study was to assess whether recreational marijuana legalization was associated with an increase in marijuana-associated calls and reduction in synthetic

cannabinoid-associated calls by using the ratio of synthetic cannabinoid records to marijuana records in NPDS. I applied a longitudinal time series design to synthetic cannabinoid to marijuana ratio trends captured by NPDS records. Our working hypotheses are that trends in marijuana-related NPDS records would increase upon recreational marijuana legalization and that synthetic cannabinoid-related NPDS records would be attenuated during the same period.

4.2 Methods

Study location

With the exception of several large cities, recreational marijuana use laws are enacted and enforced at the state level, so comparisons can be made within the state (pre- and post-intervention) and among states with and without recreational marijuana laws. There are three main categorizations of marijuana use laws across the country. The most lenient of marijuana laws is the legalization of recreational marijuana, which allows for licensed retailers to sell regulated marijuana within the state. States that pass recreational marijuana laws also generally allow individuals to grow their own marijuana. Other states have opted for a more restrictive approach and only legalize the use of marijuana for medical purposes. States that enact medical marijuana laws also generally decriminalize the possession of marijuana up to a certain amount. States that have not passed any recreational or medical marijuana laws are considered 'marijuana prohibition states', and do not allow the use, possession, or sale of marijuana products in the state.

Three states were chosen as a part of this study to reflect the three categorizations of marijuana laws. State A legalized recreational marijuana use for people over 21 years old in December 2012 and is the intervention state in this study. Twenty four months before and after

the date of state A recreational marijuana legalization was chosen as the study period, from January 1, 2010 to December 31, 2014. The second state chosen (state B) legalized medical marijuana use in winter 2009 which is outside of the study period. State B still prohibits recreational use of marijuana and was chosen as one of the control states for this study. The third state chosen (state C) prohibits both medical and recreational marijuana use and was chosen as the other control state for this study. All three states are close in proximity and have comparable demographics and poison center utilization rates per 100,000 population (Table 4-1).

Data Source

NPDS captures standardized information on each call received by a poison center including the implicated substance of exposure, patient demographics, and clinical and case management data. Each NPDS record is assigned a specific substance code to identify the substance(s) of exposure and enable surveillance. NPDS users can query the data using a combination of substance codes, clinical data, and health outcomes (Mowry, Spyker, Cantilena, McMillan, & Ford, 2014). For this study, monthly marijuana-associated calls and synthetic cannabinoid-associated calls were queried from NPDS for the 48-month study period, from January 1, 2010 to December 31, 2014, by state. Calls reporting exposure to multiple substances and calls deemed to be confirmed non-exposures by poison center staff were excluded from the study.

Measures

The dependent variable for this study was the ratio of synthetic cannabinoid-associated records to marijuana-associated records per month for each state. A synthetic cannabinoid-

associated record was defined as an NPDS record where the patient reported exposure to a synthetic cannabinoid substance, including K2, Spice, JWH-018, etc. A marijuana-associated NPDS record was defined as an NPDS record where the patient reported exposure to a marijuana substance, such as marijuana edibles or marijuana smoke. Using a ratio as the dependent variable has several advantages compared to using absolute counts or call rates per population. Poison center utilization varies by time and state so absolute counts or rates by population would be highly dependent upon the number of people who know about poison centers and choose to use poison centers when seeking healthcare. A ratio of the two groups of substances will allow for a measure that inherently addresses changes in overall poison center utilization. This measure allows for a more valid comparison between pre- and post-intervention periods and among states. Moreover, the effect of the substitution of synthetic cannabinoids to marijuana following recreational marijuana legalization in each state can be measured using the magnitude of change in ratio.

The independent variable was the month and year that recreational marijuana legislation was applied in state A.

Analysis

Our approach to analysis was the estimation of segmented time series regressions on trends in the synthetic cannabinoid to marijuana ratio over a 48-month study period. A time series of 48 months of ratios was computed for all three states. Equivalent regression models were also specified and estimated for all three states. The intervention month for state B and C was defined as the mid-point of the 48 month time series (December 2012).

Model specification included a constant and terms for: pre-intervention trend in ratio, change in ratio during the intervention month, and change in trend between the pre- and post-intervention periods. First-order autocorrelated errors were assumed in model specification. The specific regression model fitted to the data was:

$$Ratio_t = \beta_0 + \beta_1 * time_t + \beta_2 * intervention_t + \beta_3 * time\ after\ intervention_t + e_t \qquad \textit{for state A}$$

Where:

- $Ratio_t$ is the ratio of synthetic cannabinoid to marijuana-associated NPDS records
- β_0 estimates the baseline ratio at the beginning of the study period
- β_1 estimates the change in ratios that occur with each month during the pre-intervention period
- $Time_t$ is a continuous variable indicating the number of months into the study period. The total study period was 48 months.
- β_2 estimates that change in the ratio immediately following recreational marijuana legalization
- β_3 estimates the change in trend after legalization compared to the slope before legalization
- Time after $intervention_t$ is a continuous variable indicating the number of months after legalization. This is coded as zero during the pre-intervention period.
- e_t represents the random error.

The hypotheses for this study include: 1) the ratio would not significantly change each month among all three states during the pre-intervention period, 2) the ratio in the intervention month would not significantly decrease and the pre-intervention trend will be sustained in the post-intervention period for the state with medical marijuana legalization (state B) and marijuana prohibition (state C), and 3) the ratio in the intervention month would significantly decrease and the pre-intervention trend will be attenuated in the post-intervention period for the state with recreational marijuana legalization (state A). An alpha level of 0.05 was considered significant. Data management and analysis were performed in SAS 9.3 (SAS Institute, Cary, NC).

4.3 Results

There were a total of 425 synthetic cannabinoid-associated calls in state A, 153 in state B, and 207 in state C during the study period. There were a total of 662 marijuana-associated calls in state A, 115 in state B, and 178 in state C. The monthly synthetic cannabinoid to marijuana ratio for state A ranged between 0.071 and 2.00 synthetic cannabinoid records per marijuana record with a median of 0.60. The monthly ratio for state B ranged between 0.25 and 3.00 with a median of 1.58. The monthly ratio for state C ranged between 0.14 and 3.33 with a median of 1.50. The monthly ratios for states A, B, and C during the study period are displayed in Figure 4-1.

The corresponding estimates and 95% confidence intervals of the synthetic cannabinoid to marijuana ratio per month for the time series are displayed in Figure 4-2. In the 24-month pre-intervention period, there was some variability between the trends seen in the states studied. The ratio decreased by -0.010 per month for state A ($p=0.001$) while the ratio increased by 0.010 per month for state B ($p=0.047$). The ratio increased by 0.012 per month for state C during the same period but this trend was not statistically significant ($p=0.66$). These estimates suggest that during the pre-intervention period, state A had a decreasing ratio of records while state B had a slightly increasing ratio during the pre-intervention period.

The effect of recreational marijuana legalization in state A on the synthetic cannabinoid to marijuana ratio was immediate. In the recreational marijuana legalization month (month 25), state A had a drastic -0.52 decrease in the ratio ($p <0.001$, Figure 4-2). This finding suggests there may be a substitution effect directly following legalization as synthetic cannabinoid-associated records decreased and marijuana-associated records increased. A similar smaller

effect was seen in both of the control states but both findings were not significant. State B saw a -0.015 decrease in the ratio (p=0.87) and state C saw a -0.11 decrease in ratio (p=0.81).

The pre-intervention trend of synthetic cannabinoid to marijuana ratios was not attenuated in the post-intervention period for state A. While the trend in state A was a decrease of -0.01 per month in the pre-intervention period, the trend was an increase of 0.002 per month in the post-intervention period, although this finding was not significant (p=0.65). These results suggest that the immediate effect of recreational marijuana legalization in state A was not persistent in the post-intervention period.

The pre-intervention trend of synthetic cannabinoid to marijuana ratios was attenuated in the post-intervention for state B (the medical marijuana legalization state). While the trend in state B was an increase of -0.01 per month in the pre-intervention period, the trend was a decrease of -0.026 per month in the post-intervention period (p<0.001). State C also had a slight decrease in ratio of -0.008 in the post-intervention period but this finding was not significant (p=0.84).

Figure 4-3 displays the observed 48-month trends in synthetic cannabinoid to marijuana ratio and the pre-intervention trends (months 1-24) projected into the post-intervention study period for state A. Twenty-four months after recreational marijuana legalization, the observed ratio was 54.3% less than the projected ratio. For both states B and C, the observed ratio was higher than projected.

4.4 Discussion

The objective of this study was to use NPDS records to assess whether recreational marijuana legalization is associated with a reduction in synthetic cannabinoid- associated calls and an increase in marijuana- associated calls. Instead of absolute counts we used ratios of NPDS records to assess the amount of substitution from synthetic cannabinoids to marijuana. This measure also accounted for differences in poison center utilization and population over time among states. For comparison, I observed trends in a state with existing medical marijuana legislation and a state with marijuana prohibition during the 48-month study period.

State A saw a decrease in synthetic cannabinoid to marijuana ratio following legalization of recreational marijuana. The effect was immediate as evidenced by the drastic ratio decrease in state A in the month following legalization. However, the effect was not persistent as the trend slightly increased during the months after legalization. Despite the lack of a persistent effect, there was an overall decrease in ratio over the 48-month study period as a result of legalization. When the pre-intervention trend was projected into the post-intervention period for state A, the projected ratio in the last month of the study period was found to be more than twice as high as what was observed.

Alternatively, there were no significant changes in trend in states B and C in the month following legalization. The absence of a similar trend in the comparison states suggests that the immediate decreases in trend following legalization in state A are unlikely due to other external factors that would also affect states B and C.

There have not been similar studies examining the relationship between synthetic cannabinoids and marijuana at the individual state level, but these findings corroborate studies

examining the substitution effect of other drugs of abuse. For example, studies have shown that state policies leading to reductions in the availability of prescription opioids for abuse were associated with increases in heroin use trends (Dart, Surratt, & Cicero, 2015; Blumenschein, Fink, & Freeman, 2010). Individuals looking for a similar high, either in the case of opioids and heroin or synthetic cannabinoids and marijuana, may likely choose the least restricted and more freely available option amid changing state laws and policies. More studies are needed to assess the amount of expected substitution from synthetic cannabinoids to marijuana as a consequence of marijuana legislation and whether this phenomenon is present at the national level.

In this study, I demonstrated that a quasi-experimental time series design using multiple comparison groups on NPDS records could be used to assess the effects of state legislation on licit and illicit drug use. This type of study design is also rigorous enough to rule out many factors other than recreational marijuana legalization that would have led to changing trends. A new measure was also created – the ratio of records in NPDS – that adjusts for many different factors such as poison center utilization and changing population rates that can account for variation in monthly synthetic cannabinoid- and heroin-associated records. This study provides a basic framework for study design and how to create valid measures for future studies examining changing trends from state legislation using NPDS records.

There are several limitations to the study. The trends for the intervention and control states were not similar during the pre-intervention phase which may suggest that the comparison states may not have been experiencing similar synthetic cannabinoid and marijuana trends before legalization. Moreover, state B saw a persistent change in ratio in the

post-intervention period. This may reflect a delayed or gradual shift to marijuana from synthetic cannabinoids following medical marijuana legalization. Further studies examining state-specific trends in comparison to all state public health interventions or policies that may affect synthetic cannabinoid or marijuana use is needed to clarify this uncertainty.

The immediate effects of recreational marijuana legalization on the synthetic cannabinoid to marijuana ratios in state A suggest that relaxing marijuana laws may attenuate the substitution of marijuana for synthetic marijuana at the state level. The approaches in this paper provide a framework for detecting changing trends in NPDS records for assessment of state policies such as marijuana legalization. Future research should focus identifying particular state policies that are more effective in contributing to decreasing synthetic cannabinoid trends.

4.5 References

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Table 4-1. Demographic and Poison center utilization characteristics of states in the study.*

State Characteristic	Intervention State A (Recreational MJ)	Control State B (Medical MJ)	Control State C (MJ Prohibition)
Population	6.7 million	2.9 million	3.0 million
Age			
Persons under 5, percent	6.5%	6.9%	8.4%
Persons over 18, percent	23.5%	24.6%	30.5%
Race			
White, percent	77.3%	66.2%	86.1%
Black, percent	3.6%	8.1%	1.3%
Economy			
Median household income, dollars	$60,000	$52,000	$60,000
Persons in poverty, percent	13.2%	15.2%	11.7%
Total unemployment rate, percent	8.1%	11.2%	5.4%
Poison center utilization per year for 2010 (per 100,000 population)	1,159	1,939	1,890

*Data obtained from the 2010 United States Census Bureau and Bureau of Labor Statistics.
MJ = marijuana

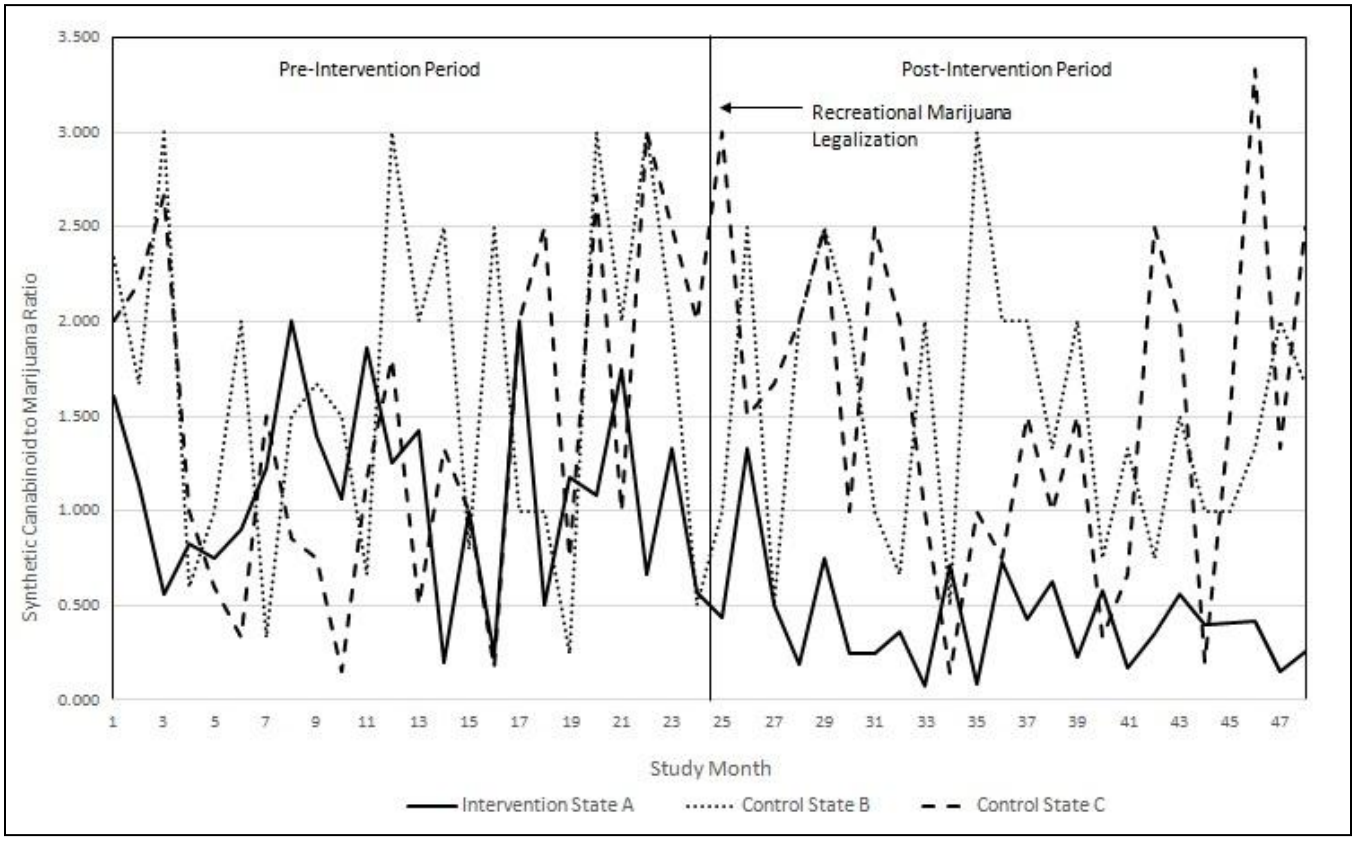

Figure 4-1. Observed trends in synthetic cannabinoid to marijuana ratios in a state that legalized recreational marijuana (State A), a state that legalized medical marijuana (State B), and a state with marijuana prohibition (State C).

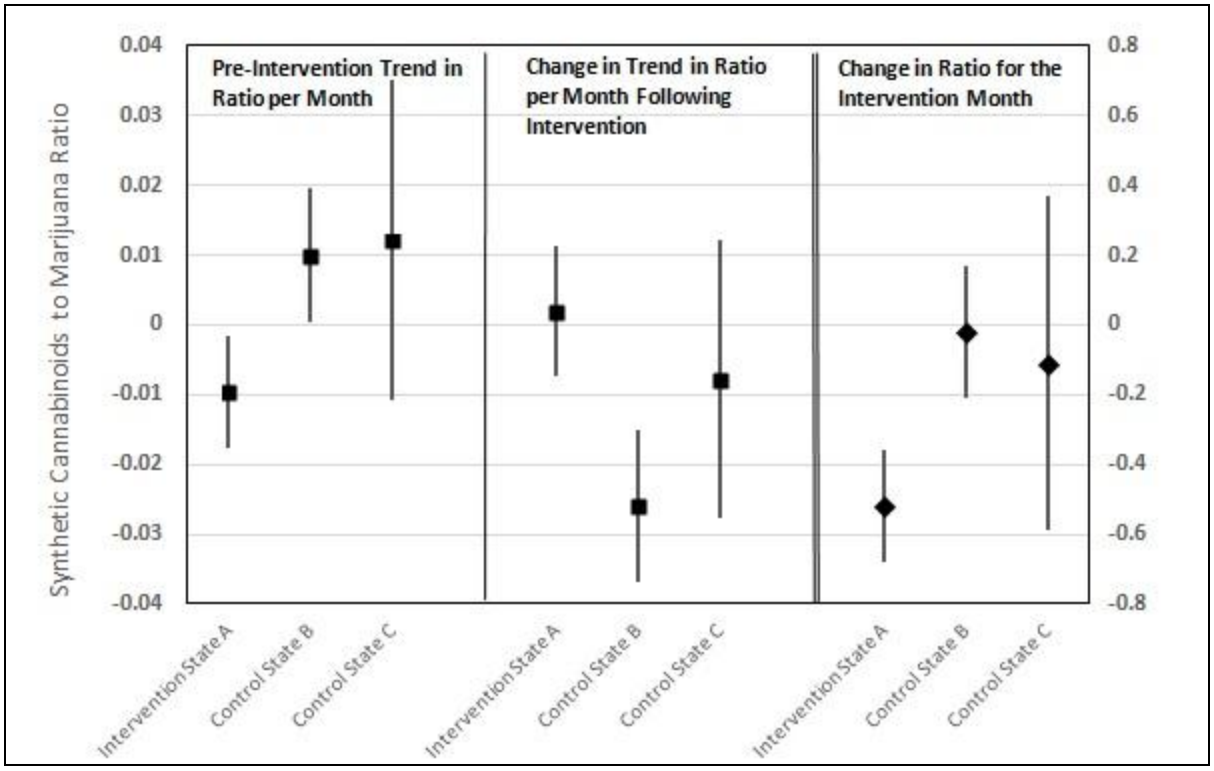

Figure 4-2. Estimates for the effects of legalizing recreational marijuana on synthetic cannabinoid and marijuana ratios in a state that legalized recreational marijuana (State A), a state that legalized medical marijuana (State B), and a state with marijuana prohibition (State C).

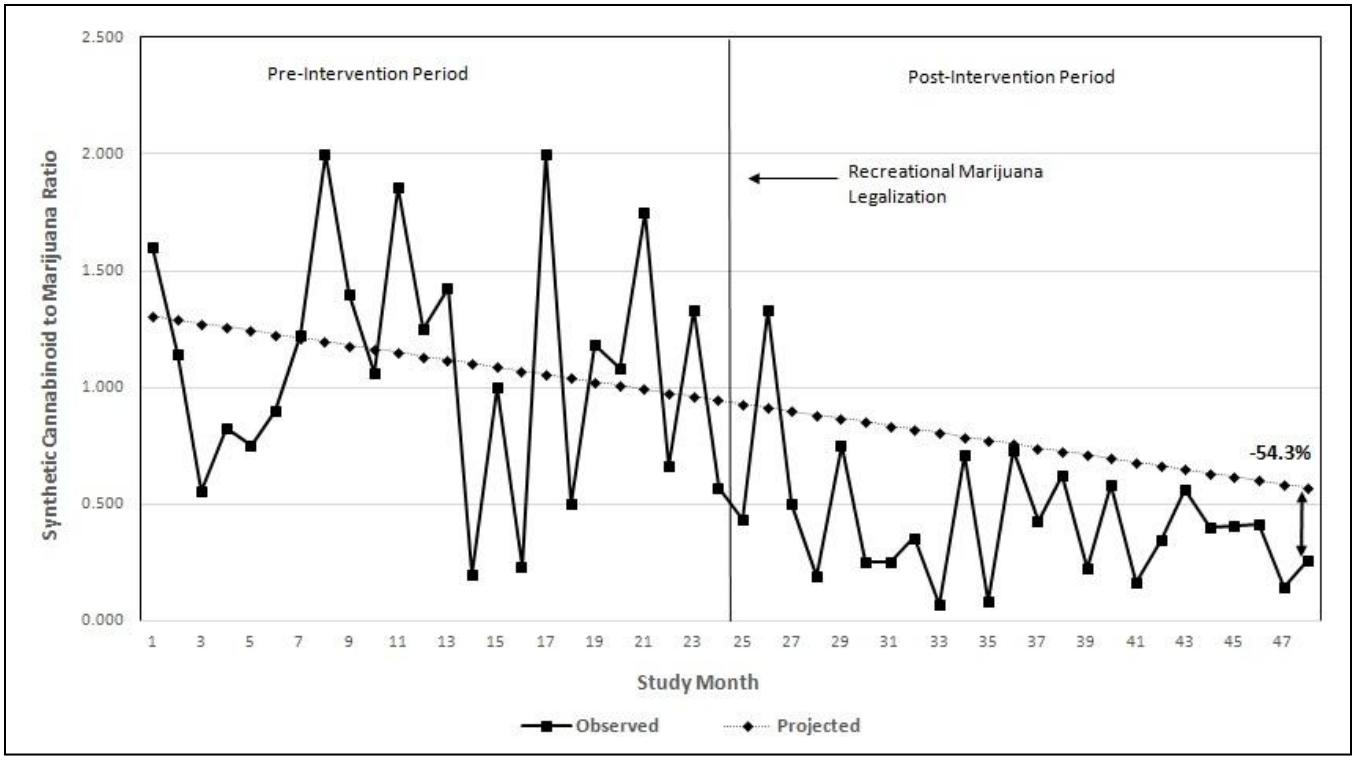

Figure 4-3. Observed trends in synthetic cannabinoid and marijuana ratios and projected trends based on pre-intervention ratios for the state with legalizing recreational marijuana.

Chapter 5: Summary

5.1 Summary

The studies presented in the dissertation explore new ways for poison center records to be used for early identification of public health threats. Syndromic surveillance is a high priority for public health officials at the local, state, and federal level in prospectively identifying threats and initiating a timely public health response. Use of a syndromic surveillance data source such as poison center records allows for timely accessibility and interpretation of data for public health decision-making.

The studies presented also explore ways for poison center records to be used for evaluating policy and program impact by identifying changing trends in poison center records. This is very different from detecting acute threats as changing trends may be subtle and be over longer time periods. Validation of these approaches in using poison center data for identification of changing trends allows for timely evaluation of policies and programs, which is critical for informing researchers, policy-makers, and public health of the intended and unintended consequences of public health and policy actions.

The goals of the studies were 1) to assess whether poison center records can be used for surveillance of noninfectious FBDOs and assess whether certain features of poison center records are more likely associated with a confirmed noninfectious FBDO, 2) to assess whether state public health interventions such as prescription drug monitoring programs were associated with a reduction in opioid use trends, and 3) to assess whether state legislation such as recreational marijuana legalization was associated with an increase in marijuana and reduction in synthetic cannabinoid use trends.

The results of the first study indicated that NPDS did capture a significant percentage of noninfectious foodborne outbreak events and illnesses. Over the ten-year study period, I found that 31% of noninfectious FBDOs in a national dataset of confirmed noninfectious outbreaks corresponded with a NPDS record by location, etiology, and time. The particular features more likely related to a confirmed FBDO included records that were related to marine toxins, had more severe outcomes, and had healthcare professional callers instead of the lay public. Detection of noninfectious FBDOs using poison center records is representative of and timelier than other established surveillance systems. Thus, poison center records could be used for rapid detections of and response to potentially serious noninfectious FBDOs.

In the second and third studies, I demonstrated that a quasi-experimental time series design with a comparison group using poison center records could be used to assess the effects of state intervention policies and legislative changes. This type of study design is also rigorous enough to rule out many factors other than the intervention that would have led to changing trends. A new measure was also created – the ratio of records – that adjusted for many different factors such as poison center utilization and changing population rates.

The results of the second study showed that poison center records were able to detect an immediate and persistent decreasing trend of opioid-related records in a state following state-wide implementation of a prescription drug monitoring program. The findings suggested we would expect twice as many opioid-related calls to poison centers had the state not implemented the program. However, the decrease in opioid trend was associated with an increase in a heroin trend. This analysis demonstrated the use of poison center records as a means to assess the intended impact of a PDMP but also an important unintended effect – that

is, the increased use of an illegal drug for which other surveillance data are not readily available.

The results of the third study showed that poison center records were able to detect an immediate decrease in trend of synthetic cannabinoid-related records in a state following state legalization of recreational marijuana use. This analysis demonstrated the use of poison center records as a means to assess an unintended effect of decreased illegal drug use for which other surveillance data may likely not capture.

The approach and findings from these three studies expand upon current knowledge of how poison center records can be used for syndromic surveillance and provide evidence that justifies expansion of poison center surveillance into avenues not yet explored by local, state, and federal public health.

5.2 Implications for future research

The existing literature shows many examples how poison centers in their routine operations collect information that is vital to public health surveillance and response. Examples include a variety of public health surveillance purposes at the local, state, federal, and international levels (Spiller & Griffith, 2009). Poison center records have been used to detect threats or monitor emergence of trends in: 1) cases of drug and substance abuse (Law, Schier, Martin, Chang, & Wolkin, 2015; Kasper & Ridpath, 2015; Hughes, Bodgan, & Dart, 2007; Rosenson, Smollin, Sporer, Blanc, & Olson, 2007; Dart, Surratt, & Cicero, 2015), 2) foodborne illness outbreaks (Derby, McNally, & Ranger-Moore, 2005; Wolkin, Martin, Law, & Schier, 2011; Gruber, Bailey, & Kowalcyk, 2015), 3) product and medication contamination (Wolkin, Martin, Law, & Schier, 2011; Gryzlak, R, Zimmerman, & Nisly, 2007), and 4) injuries from commercial

and consumer products (Chatham-Stephens, Law, & Taylor, 2014; Pillai, Law, Beuhler, & Henretig, 2012). Additionally, poison center records have been used to monitor selected illnesses in the general population (e.g., influenza), and for situational awareness following known man-made or natural disasters (Simone & Spiller, 2010; Kay, Blackmore, & Schauben, 2006; Clower, Henretig, & Trella, 2012).

The studies above cite the many strengths to using poison center records for syndromic surveillance. One major strength is that poison centers capture a population that is not captured in traditional surveillance systems. Traditional systems rely on collection of data from a person at a time and location when the person presents to an outpatient clinic or emergency room for treatment. Poison centers capture health data from a portion of the population that have not yet or may not ever see a physician or go to the emergency room for an illness (Derby, McNally, & Ranger-Moore, 2005; Spiller & Griffith, 2009). Thus the uniqueness of poison center records is to have information not necessarily available in other surveillance systems and to have it in a timely manner. The studies provide basic frameworks for interpreting this information in poison center records for public health decision-making. Future studies should focus on further understanding the population captured by poison center records and how to best leverage this data source for both identification of threats not captured in other systems and timelier capture of known public health threats.

Syndromic surveillance data such as data collected by poison centers are typically analyzed using traditional aberration detection methods (Fricker, 2013). Techniques include statistical process control such as the historical limits method, cumulative sum (CUSUM) method, and change point analyses (Hennig, 2004; Provincial Infectious Diseases Advisory

Committee, 2012). The studies I conducted demonstrate that these data can be evaluated and provide insight into population health trends by using health services research methods such as interrupted time series. The knowledge gained opens the door for many research opportunities including: evaluation of public health intervention effectiveness, assessment of intended and unintended consequences following state legislative or public health actions, assessment of differences in state trends following national legislative or public health actions, and comparative analyses between states.

5.3 Future research directions

Poison center data representativeness

There are 55 poison centers which service all of the United States and US territories. Poison centers are available to residents of all state and territories and civilian and military personnel abroad, as long as they have telephone access. Geographically, poison center service area and resultant poison center records are fully representative.

There have been many studies examining the correlations between the rate of poison center calls and health outcomes such as emergency department encounter rates and death rates. Studies have shown that poison center calls and emergency department encounters are highly correlated for a variety of exposure types, including disaster-related exposures (Clower, Henretig, & Trella, 2012; Kay, Blackmore, & Schauben, 2006), and pharmaceutical drugs (Naun, Olsen, & Dean, 2011). Specifically for this dissertation, increases in poison center calls related to pharmaceutical opioids and heroin are correlated with increases in emergency department visits for these substances (Dart, Surratt, & Cicero, 2015). There are similar findings in studies examining synthetic cannabinoid and marijuana exposures (Kasper & Ridpath, 2015).

However, the literature is less clear regarding the proportion of poison center calls that represent the universe of exposures that occur in the US. For example, if there are 50 callers to poison centers about illness from synthetic cannabinoids, we ideally could estimate how many exposures are occurring in the population. Persons exposed to a toxic substance do not necessarily seek care by calling poison centers. In exposures with very severe clinical effects, care is more likely sought at emergency departments and not routinely reported to poison centers unless the attending physician requires toxicological consultation from the poison center. Moreover, poison centers are called for acute exposures and are less likely called for more chronic exposures. Thus, poison centers do not capture all exposure events; the ability to capture depends on whether users call and depends on the implicated substance in question.

A broad set of published studies helps bridge the gap between poison center utilization and its representativeness to the population. From an Institute of Medicine report (2005), direct review of hospital charts demonstrated that about 20 to 30 percent of poisoning cases managed in the emergency department are reported to poison centers. From a Consumer Product Safety Commission report (2000) on the National Electronic Injury Surveillance System (NEISS), a poison center was called before a hospital visit in one-third of children's poisonings treated in an emergency department. The findings of Setlik at al. (2010) suggest that poison center data are very representative for unintentional pharmaceutical exposures in children less than four years of age. In examining health care facility records from 2001–2003, the authors found that the number of poison center records was actually greater than the NEISS point estimate for the number of exposures in the United States, but within the 95% confidence interval.

Another important consideration for representativeness is poison center use across different population segments. Litovitz et al. (2010) sought positive and negative factors affecting use of a poison center. Negative predictors included inability to speak English well and black/African American race. Positive predictors included the percentage of the population aged less than five years, percentage of the adult population with a bachelor's degree, Asian population percentage, and population density. Kelly et al. (1997) corroborated those findings. They identified two factors associated with not using poison center services: black/African American race and schooling outside the United States.

Thus, even though poison centers cover a service area that spans the entire US, not all exposures are called to poison centers. Representativeness issues arise and certain population segments are over- or under-represented based on substance of exposure and determinants to use. Studies show strong correlations between poison center call volumes and health outcomes, which can provide the necessary context in deriving conclusions when analyzing and interpreting poison center data. But deriving estimations of the proportions of the population affected by using poison center records is a direction for future research. Given these considerations, further research should focus on quantifying the representativeness of poison center data on exposures in the US and other health outcomes such as emergency department visits and deaths.

Creation and evaluation of multivariate algorithms for syndromic surveillance

The first study provided evidence that certain features of poison center records are more likely related to an outbreak such as case severity. The value of poison center records is that these types of records may aid in more timely capture of outbreaks. This is likely the case

for not only noninfectious foodborne illnesses, as records related to illicit drugs, infectious foodborne exposures and toxic gas-related exposures may also have underlying features that make them more likely related to an incident that requires public health action (Derby, McNally, & Ranger-Moore, 2005; Wolkin, Martin, Law, & Schier, 2011; Law, Schier, Martin, Chang, & Wolkin, 2015). However, determination of outbreaks just by examining features of individual records does not account for temporal clustering of records which may also be an important indication of an outbreak. Combining these two variables, specific features of records and clustering of related records, to create multivariate algorithms as a part of syndromic surveillance analyses may improve outbreak detection capabilities (Syndromic Surveillance, 2015; Corberan-Vallet, 2012; Vial, Wei, & Held, 2015). Public health surveillance officials should incorporate both the temporal clustering of calls using existing statistical control methods and the particular features of calls as a part of automated syndromic surveillance algorithms to improve outbreak detection. These types of procedures are already being tested using other data sources, such as emergency department chief complaint data; compared to non-multivariate algorithms, multivariate algorithms perform better in sensitivity and timeliness while reducing the number of false positive alerts (Burkom, Elbert, & Feldman, 2004; Hefferman & Mostashari, 2004).

Currently, national surveillance activities using poison center records only use temporal clustering for outbreak detection, and some states are starting to use multivariate algorithms for syndromic surveillance (Wolkin, Martin, Law, & Schier, 2011; Florida Surveillance Systems , 2015; Oregon ESSENCE, 2015). Future research directions should evaluate which temporal clustering parameters and poison center record features will result in the highest sensitivity in

outbreak detection while minimizing alert burden, keeping in mind that these parameters may differ depending on the implicated substance of the outbreak.

Incorporating multiple data streams in syndromic surveillance

Syndromic surveillance, while timely in data collection and analysis, lacks case confirmation compared to data collected by traditional surveillance data sources. Thus, indications or alerts of an outbreak identified by syndromic surveillance may require validation by an experienced surveillance system user in order to determine the necessity of public health action (Mandl, et al., 2004; Provincial Infectious Diseases Advisory Committee, 2012). Validation activities include confirmation of data accuracy and assessment of the likelihood the alert is a true incident. For national syndromic surveillance activities using poison center records, validation of automated alerts generated by the national surveillance system currently follows a two-step process (National Chemical and Radiological Surveillance Program , 2015). In the first step, each alert needs to be verified for accuracy to ensure the data related to a cluster of calls were not collected or reported in error. This step requires reaching back to the poison center that collected the data. In the second step, a team of poison center directors work together to determine, using a standardized public health incident criteria, whether the alert elevates to a categorization of an incident of public health significance. Alerts identified as incidents of public health significance are relayed back to the state epidemiologist where the incident originated for public health action as needed. In this example, validation activities can become time-consuming and resource-intensive, particularly if the number of alerts generated by the syndromic surveillance system is high.

Increasing the confidence that an alert is related to an incident of public health significance will reduce the need for intensive validation, thereby freeing up resources for other surveillance or response activities. Incorporating multiple syndromic surveillance data streams may provide greater confidence of the presence of an outbreak. Examples of other syndromic surveillance data streams that may complement poison center records include: internet-based illness reporting, insurance triage hotlines, emergency department chief complaints, and over-the-counter medication sales (Syndromic Surveillance, 2015). Incorporation of multiple data streams for surveillance is being tested with varying complexity (from parallel analyses to Bayesian modeling) in certain state and international systems. Results from studies assessing the benefits of incorporating multiple data streams for surveillance have been generally positive (Corberan-Vallet, 2012; Vial, Wei, & Held, 2015; Faverjon, Andersson, & Decors, 2016). Using multiple data streams as opposed to single data streams has shown to increase detection sensitivity while keeping alert burden stable (Rolka, Burkom, & Cooper, 2008). However, algorithms with high complexity modeling such as Bayesian modeling have shown to have diminishing returns in providing better detection capabilities compared to simpler models because the more complex models require more computing power and longer run time (Wong & Cooper, 2005). Moreover, the potential value of poison center records has not been considered in these assessments. Future research directions in assessing effectiveness of multiple data streams should include poison center records as a part of the evaluation, and efforts in improving state and national syndromic surveillance should focus on incorporating evidence-based approaches to using multiple data streams.

Timely evaluation of state programs, policies and interventions

In my studies, state names were not used in order to maintain privacy of state-specific data. However, the methods and approaches presented here can be conducted by any state for timely evaluation of state policies and interventions. For segmented time series, the recommended number of time observations for robustness and validity of results is between fifty to one hundred observations. In the second and third study, a total time period of four years (48 months) was used to ensure validity of parameter estimates. For timelier analyses, researchers can also use weekly, daily, or even hourly observations instead of monthly observations, cutting the time to yield robust results from two years after the intervention to only days to weeks. As public health continues to move toward implementation of evidence-based programs and creating feedback mechanisms to evaluate program effectiveness, public health officials should consider poison center records as a potential source for evaluation of policies, programs, and interventions.

5.4 Conclusion

There has been a gradual shift toward using non-traditional but rapidly available syndromic surveillance data such as poison center records in routine detection of public health issues (Derby, McNally, & Ranger-Moore, 2005; Hughes, Bodgan, & Dart, 2007). Researchers and public health officials understand that innovation and adaptation of new data sources into public health surveillance is necessary as electronic medical record systems evolve and health information represents care provided outside hospital and clinic settings. My studies demonstrated how poison center records can be better integrated to syndromic surveillance research. Continued work to integrate 'non-hospital' data into syndromic surveillance will lead

to more responsive and informed public health systems and will move us towards the ultimate goal of reducing morbidity and mortality and improving population health outcomes.

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